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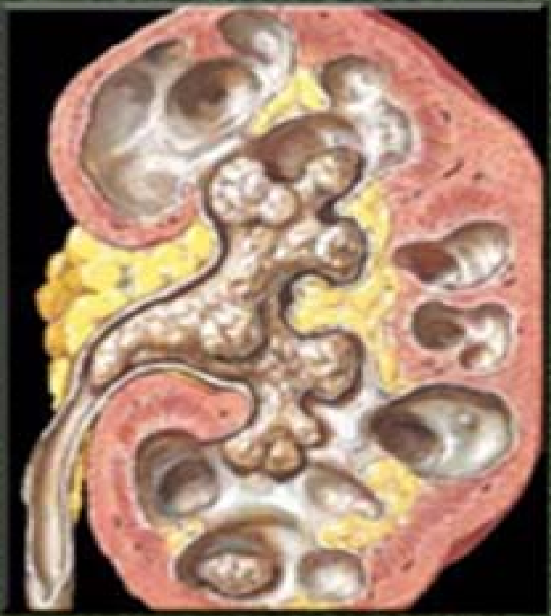
FRANK H. NETTER, MD 2nd Edition

VOLUME 5



Urinary System

CHRISTOPHER R. KELLY
JAIME LANDMAN

SAUNDERS
ELSEVIER

VOLUME 5

The Netter Collection
OF MEDICAL ILLUSTRATIONS
Urinary System

2nd Edition

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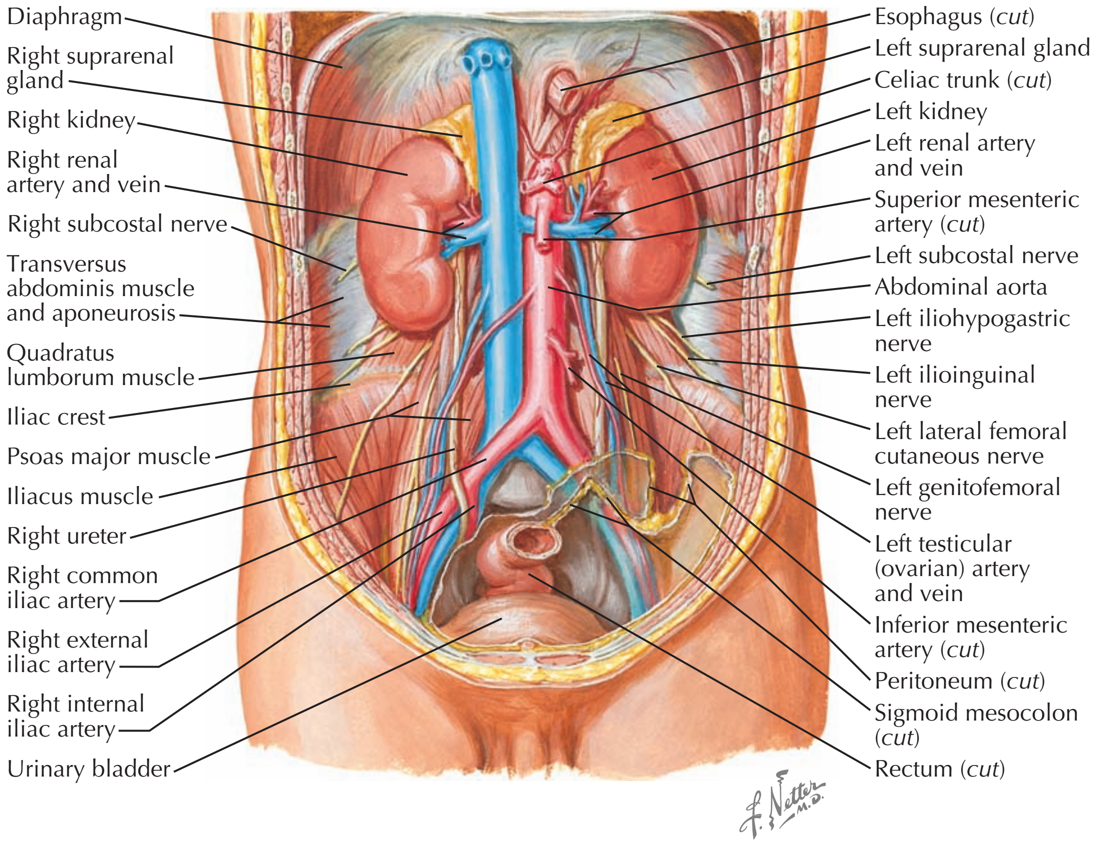
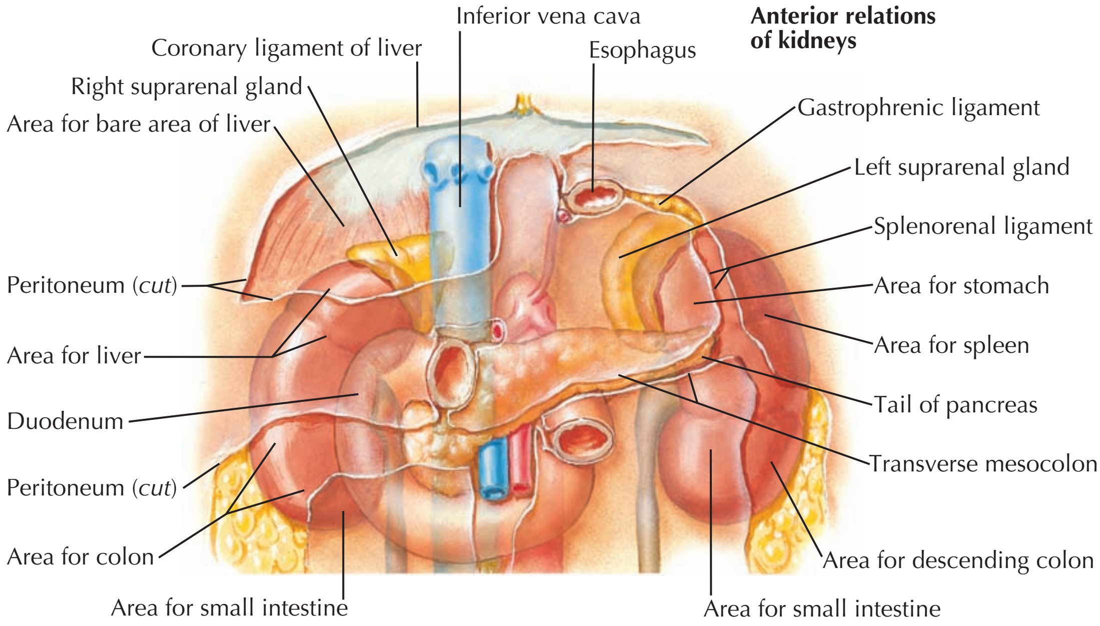
SECTION 1

ANATOMY OF THE URINARY TRACT

Position and Relations of Kidney: Anterior Views


Diaphragm
Right suprarenal gland
Right kidney
Right renal artery and vein
Right subcostal nerve
Transversus abdominis muscle and aponeurosis
Quadratus lumborum muscle
Iliac crest
Psoas major muscle
Iliacus muscle
Right ureter
Right common iliac artery
Right external iliac artery
Right internal iliac artery
Urinary bladder
Esophagus (*cut*)
Left suprarenal gland
Celiac trunk (*cut*)
Left kidney
Left renal artery and vein
Superior mesenteric artery (*cut*)
Left subcostal nerve
Abdominal aorta
Left iliohypogastric nerve
Left ilioinguinal nerve
Left lateral femoral cutaneous nerve
Left genitofemoral nerve
Left testicular (ovarian) artery and vein
Inferior mesenteric artery (*cut*)
Peritoneum (*cut*)
Sigmoid mesocolon (*cut*)
Rectum (*cut*)

Anterior relations of kidneys


Inferior vena cava
Coronary ligament of liver
Esophagus
Right suprarenal gland
Area for bare area of liver
Gastrophrenic ligament
Left suprarenal gland
Splenorenal ligament
Peritoneum (*cut*)
Area for stomach
Area for liver
Area for spleen
Tail of pancreas
Duodenum
Transverse mesocolon
Peritoneum (*cut*)
Area for colon
Area for descending colon
Area for small intestine
Area for small intestine

Kidney: Position and Relations

POSITION AND SHAPE

The kidneys are paired retroperitoneal organs that lie lateral to the upper lumbar vertebrae. In the relaxed, supine position, their superior poles are level with the twelfth thoracic vertebra, while their inferior poles are level with the third lumbar vertebra and about 2.5 cm superior to the iliac crest. On deep inspiration in the erect position, however, both kidneys may descend near or even past the iliac crest. Usually the right kidney lies 1 to 2 cm inferior to the left kidney because its developmental ascent is blocked by the liver.

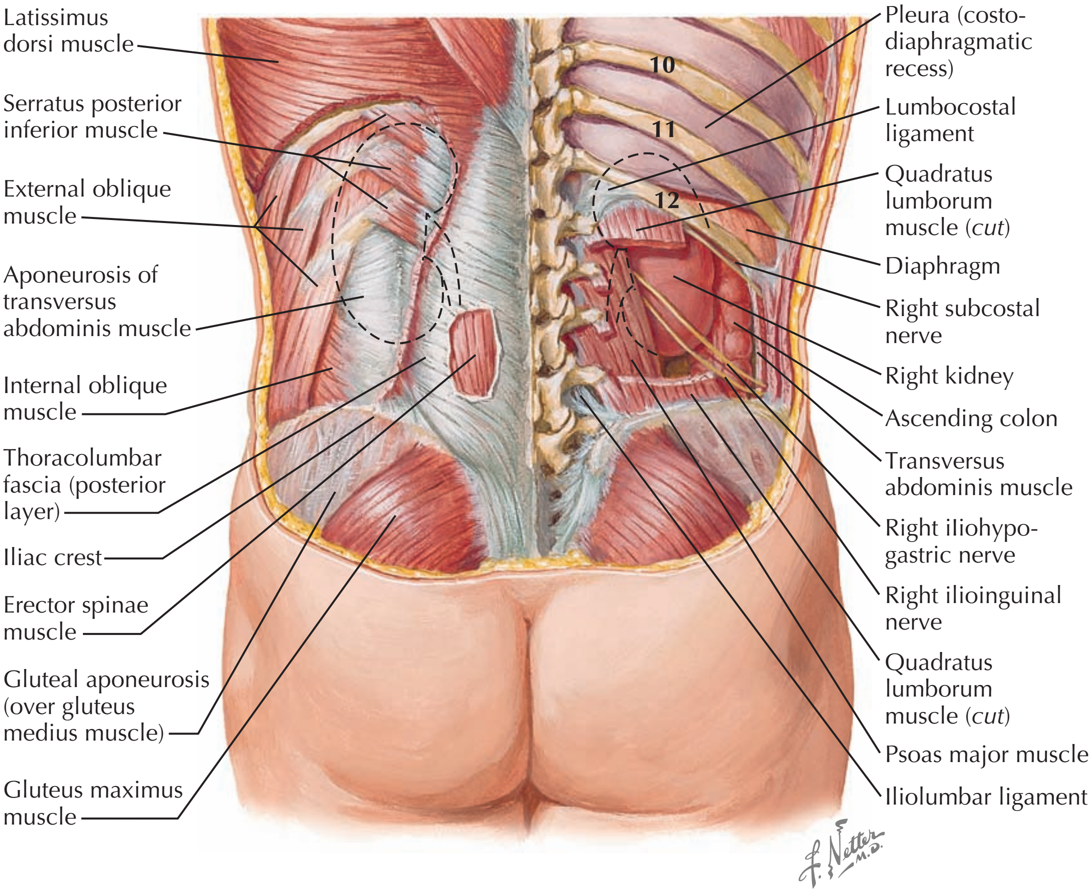
Most commonly, both kidneys are surrounded by a variable amount of retroperitoneal fat (see Plate 1-5); as in most anatomic descriptions, however, this fat is not considered in the relational descriptions that follow.

Both kidneys lie in close proximity to the abdominal aorta and inferior vena cava. These major vessels extend branches to each kidney that enter at a notched, medially located area of the parenchyma known as the hilum. At the level of the kidneys, the abdominal aorta lies directly anterior to the vertebral column, passing about 2.5 cm anteromedial to the left kidney. The inferior vena cava lies to the right of the aorta, nearly touching the medial aspect of the right kidney. Both kidneys are rotated so that their medial surfaces are slightly anterior, facilitating their connection to these major vessels.

The suprarenal glands, historically referred to as "adrenal" (a misnomer that incorrectly implied a subservient relationship to the kidneys), are bilateral glands typically related to the superomedial aspects of the kidneys but not attached to them. They are attached to the diaphragmatic crura, a relationship maintained in the presence of nephroptosis ("dropped kidneys"). Like the kidneys, the suprarenal glands are surrounded by a variable amount of fat. The crescentic left suprarenal gland lies medial to the upper third of the kidney, extending from the apex to the hilum. The pyramidal right suprarenal gland sits caplike on the superior pole of the right kidney.

The anterior relations of the left and right kidneys differ, reflecting their associations with the various unpaired organs that constitute the abdominal viscera. The posterior relations of both kidneys are similar, reflecting their associations with the paired muscles of the posterior abdominal wall.

Position and Relations of Kidney: Posterior Views


Latissimus dorsi muscle
Serratus posterior inferior muscle
External oblique muscle
Aponeurosis of transversus abdominis muscle
Internal oblique muscle
Thoracolumbar fascia (posterior layer)
Iliac crest
Erector spinae muscle
Gluteal aponeurosis (over gluteus medius muscle)
Gluteus maximus muscle
10
11
12
Pleura (costodiaphragmatic recess)
Lumbocostal ligament
Quadratus lumborum muscle (*cut*)
Diaphragm
Right subcostal nerve
Right kidney
Ascending colon
Transversus abdominis muscle
Right iliohypogastric nerve
Right ilioinguinal nerve
Quadratus lumborum muscle (*cut*)
Psoas major muscle
Iliolumbar ligament
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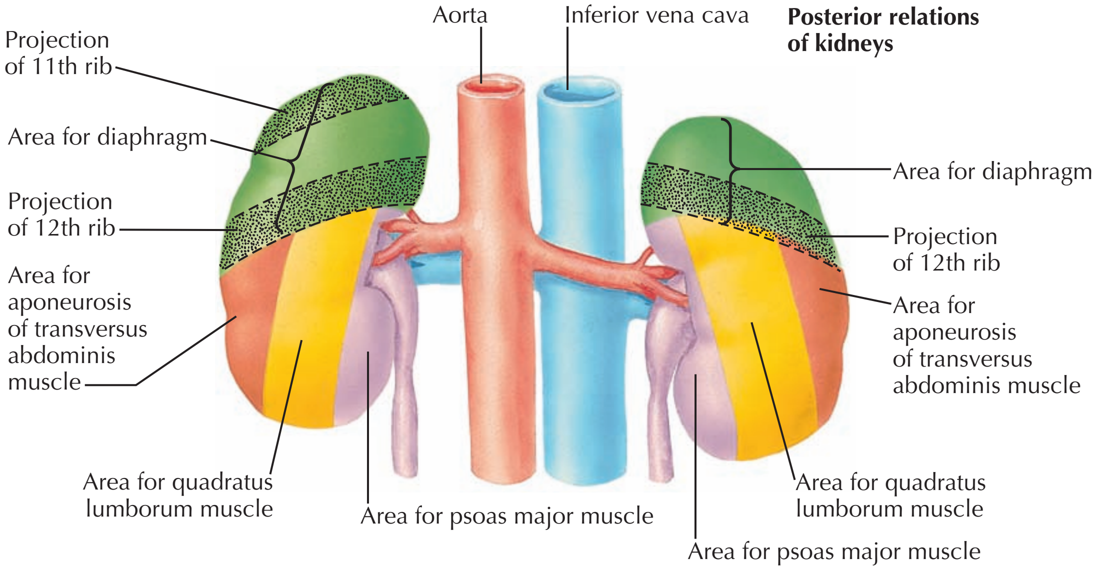

Posterior relations of kidneys
Aorta
Inferior vena cava
Projection of 11th rib
Area for diaphragm
Projection of 12th rib
Area for aponeurosis of transversus abdominis muscle
Area for quadratus lumborum muscle
Area for psoas major muscle
Area for diaphragm
Projection of 12th rib
Area for aponeurosis of transversus abdominis muscle
Area for quadratus lumborum muscle
Area for psoas major muscle

KIDNEY: POSITION AND RELATIONS *(Continued)*

ANTERIOR RELATIONS

Kidney development occurs in the retroperitoneal space on each side of a dorsal mesentery, which is initially attached along the midline of the posterior body wall. During growth of the liver and rotation of the gut, certain portions of the gut fuse to the posterior body wall and become secondarily retroperitoneal. Throughout this process, peritoneal reflections are shifted from the midline and distorted in an irregular but predictable pattern.

After development is complete, certain parts of the kidneys contact intraperitoneal organs through an intervening layer of peritoneum, whereas other parts contact primarily or secondarily retroperitoneal organs without an intervening layer of peritoneum. The presence or absence of intervening peritoneum may affect the spread of infection or metastatic disease.

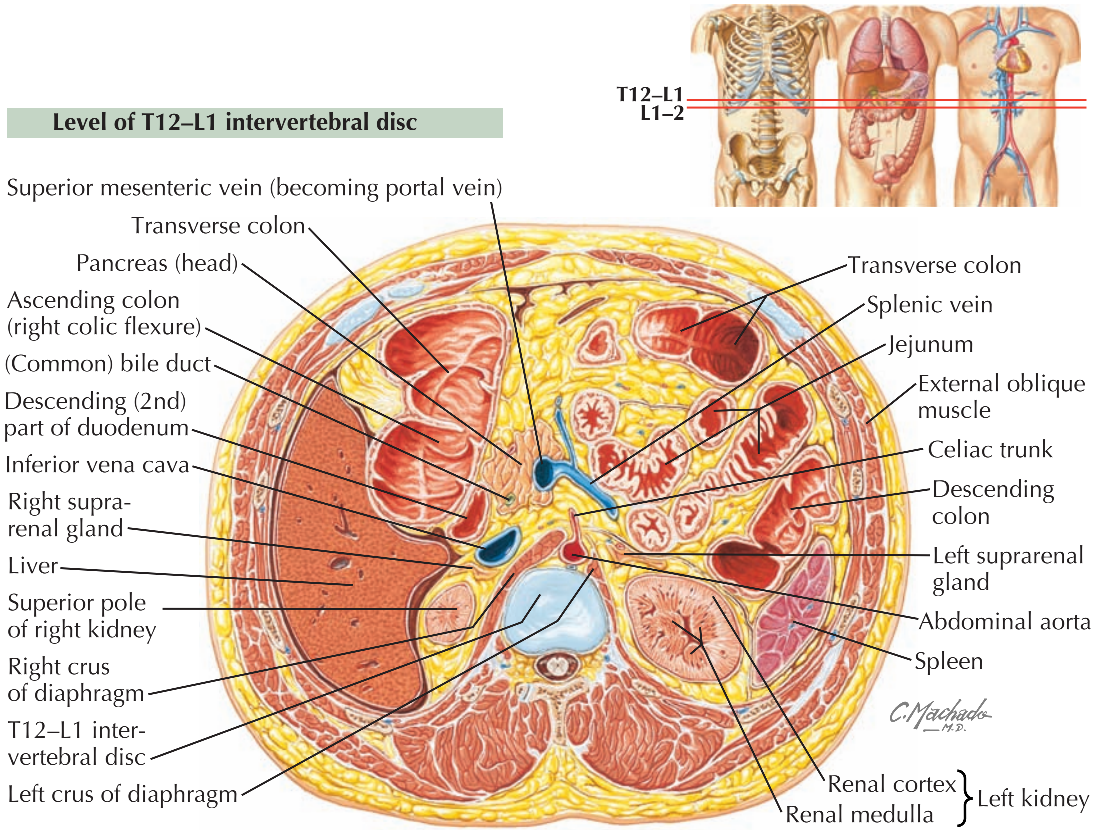
Left Kidney. The superolateral aspect of the left kidney contacts the spleen. Separating these organs is the peritoneum that forms the posterior surface of the perisplenic region of the greater peritoneal sac. A triangular area on the superomedial aspect of the left kidney contacts the stomach. Separating these organs is the peritoneum of the lesser sac (omental bursa). The splenic and gastric areas of the anterior renal surface are separated by the splenorenal ligament, a derivative of the dorsal mesentery that forms the left boundary of the lesser sac. The two layers of the peritoneum that form the splenorenal ligament enclose the splenic vessels.

The perihilar region of the left kidney contacts the tail of the pancreas, a secondary retroperitoneal organ, without intervening peritoneum. This point of contact occurs posterior to the left extremity of the transverse mesocolon, a horizontally disposed derivative of the embryonic dorsal mesentery that suspends the transverse colon from the secondarily retroperitoneal viscera (i.e., duodenum and pancreas).

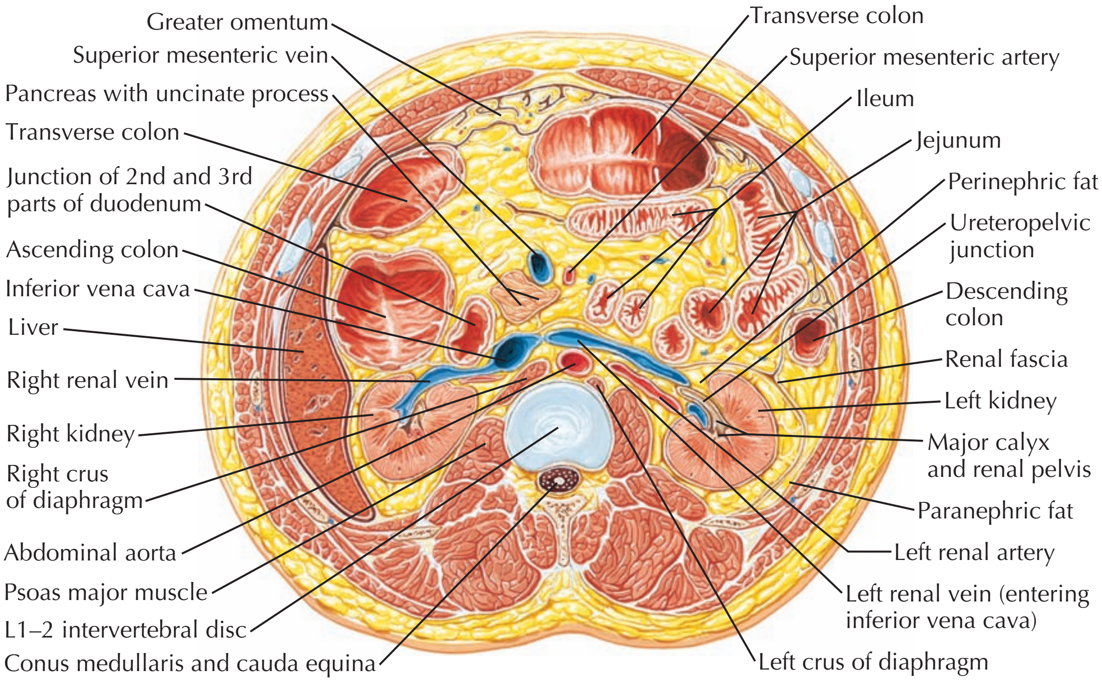
The inferolateral aspect of the left kidney contacts the descending colon, which is secondarily retroperitoneal, without intervening peritoneum. The inferomedial aspect of the left kidney contacts loops of jejunum through an intervening layer of inframesocolic peritoneum.

POSITION AND RELATIONS OF KIDNEY: TRANSVERSE SECTIONS

Level of T12–L1 intervertebral disc


T12–L1
L1–2
Superior mesenteric vein (becoming portal vein)
Transverse colon
Pancreas (head)
Ascending colon (right colic flexure)
(Common) bile duct
Descending (2nd) part of duodenum
Inferior vena cava
Right suprarenal gland
Liver
Superior pole of right kidney
Right crus of diaphragm
T12–L1 intervertebral disc
Left crus of diaphragm
Transverse colon
Splenic vein
Jejunum
External oblique muscle
Celiac trunk
Descending colon
Left suprarenal gland
Abdominal aorta
Spleen
Renal cortex
Renal medulla
Left kidney

Level of L1–2 intervertebral disc


Greater omentum
Superior mesenteric vein
Pancreas with uncinate process
Transverse colon
Junction of 2nd and 3rd parts of duodenum
Ascending colon
Inferior vena cava
Liver
Right renal vein
Right kidney
Right crus of diaphragm
Abdominal aorta
Psoas major muscle
L1–2 intervertebral disc
Conus medullaris and cauda equina
Transverse colon
Superior mesenteric artery
Ileum
Jejunum
Perinephric fat
Ureteropelvic junction
Descending colon
Renal fascia
Left kidney
Major calyx and renal pelvis
Paranephric fat
Left renal artery
Left renal vein (entering inferior vena cava)
Left crus of diaphragm

KIDNEY: POSITION AND RELATIONS *(Continued)*

Right Kidney. The upper two thirds of the right kidney contact the right lobe of the liver. The superior pole extends above the coronary ligament to directly contact the bare area of the liver without intervening peritoneum. Inferior to the pole, the kidney is covered with peritoneum that forms the posterior wall of the hepatorenal recess (also known as the Morison pouch), part of the subhepatic space of the greater peritoneal sac.

The perihilar region of the right kidney directly contacts the second (descending) part of the duodenum, which is secondarily retroperitoneal.

Most of the lower third of the right kidney is in direct contact with the right colic flexure; however, a small section of the inferior pole may contact the small intestine through a layer of inframesocolic peritoneum.

POSTERIOR RELATIONS

The approximate upper third of both kidneys contacts the diaphragm. The diaphragm normally separates the kidneys from the diaphragmatic part of the parietal pleura. On occasion, however, a deficiency in the region of the lateral arcuate ligament or the lumbocostal trigone allows one of the kidneys to directly contact the overlying diaphragmatic pleura.

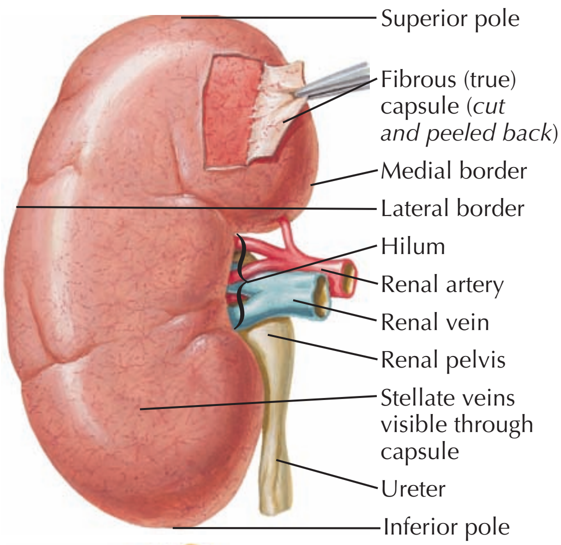
The upper third of the left kidney lies anterior to, and is thus protected by, the eleventh and twelfth left ribs. A smaller portion of the right kidney receives similar protection in its relationship to right twelfth rib.

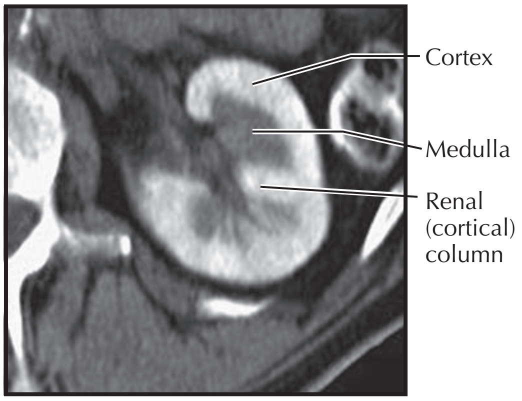
With regard to the lower two thirds of both kidneys, the lateral aspects rest on the aponeuroses of the transversus abdominis muscles; the central aspects rest on the quadratus lumborum muscles; and the medial aspects rest on the psoas muscles.

The psoas muscles take an oblique course from the lumbar vertebrae to the femurs, displacing the kidneys laterally. Because the right kidney lies inferior to the left kidney, it is generally displaced farther from the midline.

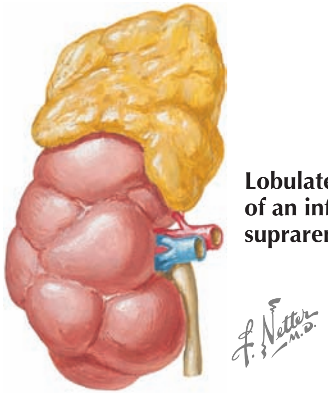
On each side, two or three nerves pass posterior to the psoas muscle, emerge from its lateral border, then travel between the kidneys and the aponeurosis of the transverse abdominis as they descend obliquely to the inguinal region. In craniocaudal order, these are the subcostal (T12 spinal) nerve and the L1 spinal nerve or its terminal branches—the iliohypogastric and the ilioinguinal nerves.

Anterior surface of right kidney

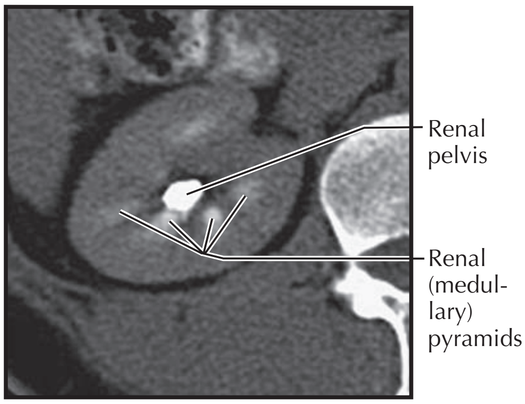

Superior pole
Fibrous (true) capsule (*cut and peeled back*)
Medial border
Lateral border
Hilum
Renal artery
Renal vein
Renal pelvis
Stellate veins visible through capsule
Ureter
Inferior pole


Cortex
Medulla
Renal (cortical) column

Computed tomography of left kidney with contrast in the cortical phase

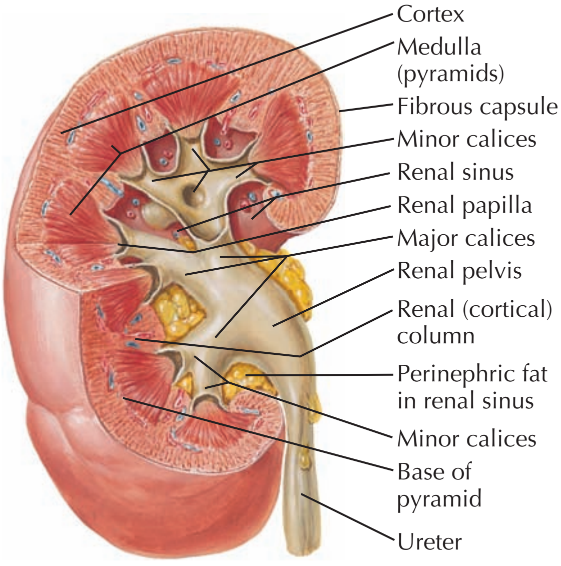


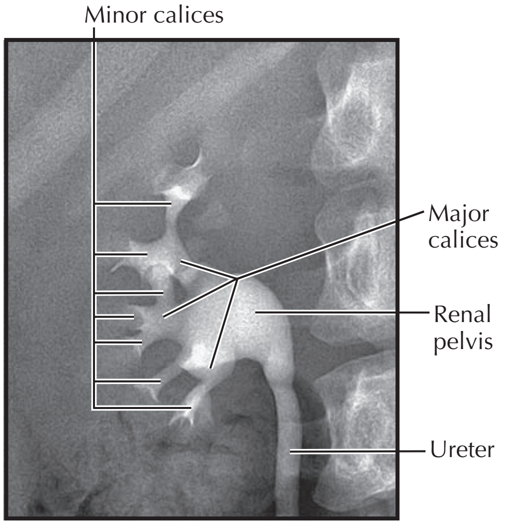
Lobulated kidney of an infant with suprarenal gland


Renal pelvis
Renal (medullary) pyramids

Computed tomography of right kidney with contrast in the excretory phase

Right kidney sectioned in several planes, exposing parenchyma and renal pelvis


Cortex
Medulla (pyramids)
Fibrous capsule
Minor calices
Renal sinus
Renal papilla
Major calices
Renal pelvis
Renal (cortical) column
Perinephric fat in renal sinus
Minor calices
Base of pyramid
Ureter


Minor calices
Major calices
Renal pelvis
Ureter

Retrograde pyelogram of the right kidney

KIDNEY: GROSS STRUCTURE

The adult kidney is about 11 cm long, 2.5 cm thick, 5 cm wide, and weighs between 120 and 170 g. The lateral border of each kidney is convex, whereas the medial border is concave. The superior and inferior poles are rounded. Both the anterior and posterior surfaces of the kidney are also convex, although the posterior surface may be relatively flattened.

The renal artery and vein, as well as the urine collecting system, enter and exit the medial aspect of each kidney at the hilum. This indented region leads to a spacious cavity within each kidney known as the renal sinus. Within the renal sinus, a matrix of perinephric fat surrounds branches of the renal artery and vein, as well as the large branches of the urinary collecting system. The veins are generally the most anterior and the branches of the collecting system most posterior, with the arteries coursing in between.

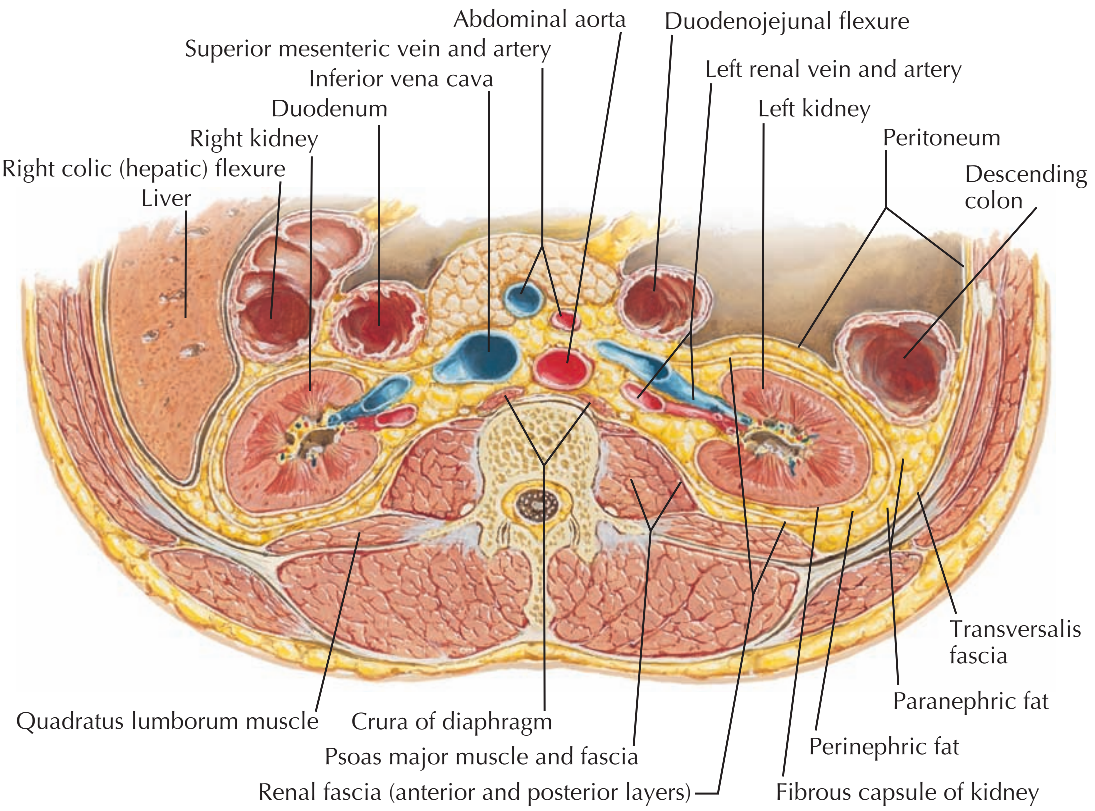
The entire outer rim of the renal parenchyma consists of a brownish pink region known as the renal cortex. Deep to the cortex, numerous darker-colored renal pyramids, with bases directed peripherally and apices directed centrally, collectively form the renal medulla. The apices of the renal pyramids are known as the renal papillae. Two or more pyramids may fuse at their papillae; thus there are more pyramids than papillae in each kidney.

The areas of cortex overlying the bases of the pyramids, separating them from the outer surface of the kidney, are known as cortical arches. The areas of cortex projecting between pyramids are known as renal (cortical) columns (of Bertin). The term “column” refers to their appearance on section; in fact, they are more like walls, which surround and separate the pyramids.

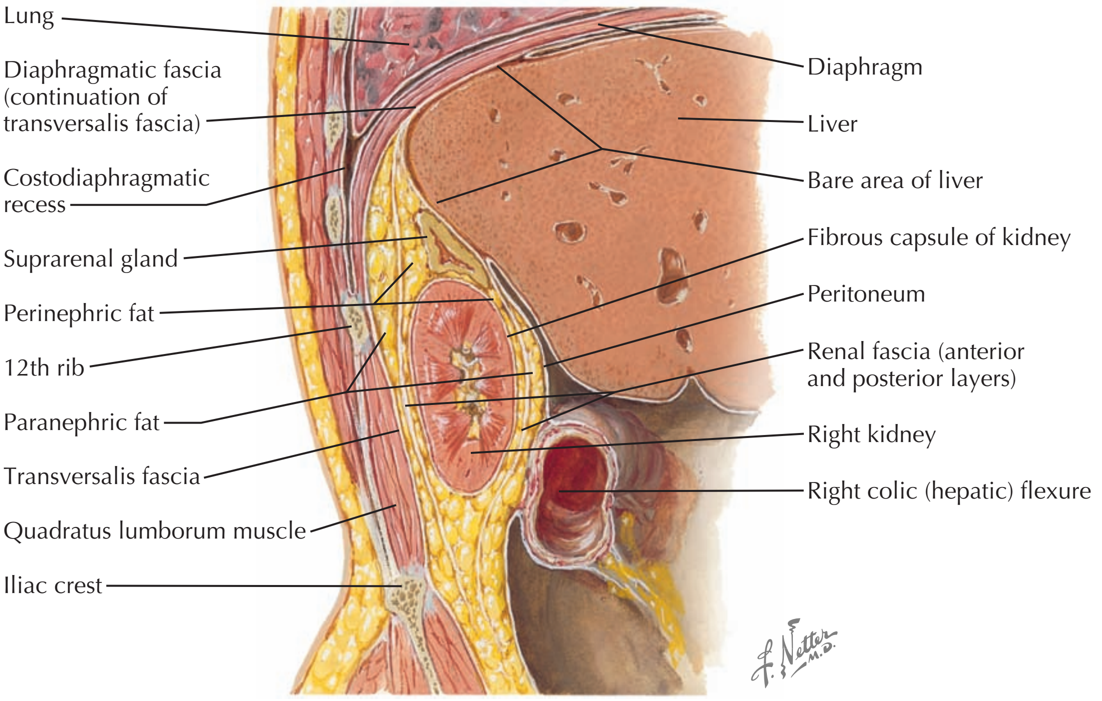
Although the borders between pyramids and renal columns are sharply defined, the pyramids project striations into the cortical arches, known as medullary rays. These striations largely represent collecting ducts (see Plate 1-26), which extend from the cortex to the renal papillae, merging along the way into papillary ducts. The papillary ducts drain urine to 20 or more small pores at each papilla’s cribriform area (area cribrosa). One to three papillae drain into each minor calyx; two to four minor calices join to form a major calyx; and two or three major calices join to form the funnel-shaped renal pelvis, which becomes the ureter after leaving the hilum. The ureter, in turn, conveys urine to the bladder for storage.

The parenchyma served by a single papilla is known as a renal lobe, and in the fetus and infant these lobes are evident as grossly visible convexities separated by deep grooves on the kidney surface. Such lobulation persists in some mammalian species throughout life, and vestigial demarcations of lobulation are occasionally present in the human adult.

Transverse section through 2nd lumbar vertebra demonstrating horizontal disposition of renal fascia


Abdominal aorta
Duodenojejunal flexure
Superior mesenteric vein and artery
Left renal vein and artery
Inferior vena cava
Duodenum
Left kidney
Right kidney
Peritoneum
Right colic (hepatic) flexure
Descending colon
Liver
Transversalis fascia
Paranephric fat
Quadratus lumborum muscle
Crura of diaphragm
Perinephric fat
Psoas major muscle and fascia
Renal fascia (anterior and posterior layers)
Fibrous capsule of kidney

Sagittal section through right kidney and lumbar region demonstrating vertical disposition of renal fascia


Lung
Diaphragmatic fascia (continuation of transversalis fascia)
Costodiaphragmatic recess
Suprarenal gland
Perinephric fat
12th rib
Paranephric fat
Transversalis fascia
Quadratus lumborum muscle
Iliac crest
Diaphragm
Liver
Bare area of liver
Fibrous capsule of kidney
Peritoneum
Renal fascia (anterior and posterior layers)
Right kidney
Right colic (hepatic) flexure
F. Netter M.D.

RENAL FASCIA

The renal parenchyma is enclosed by a thin but distinct glistening membrane known as the fibrous (true) capsule of the kidney, which extends into the renal sinus. Immediately surrounding the fibrous capsule is a variable amount of perinephric fat (perirenal fat capsule), which forms a matrix around the structures within the renal sinus. The perinephric fat also surrounds the ipsilateral suprarenal gland.

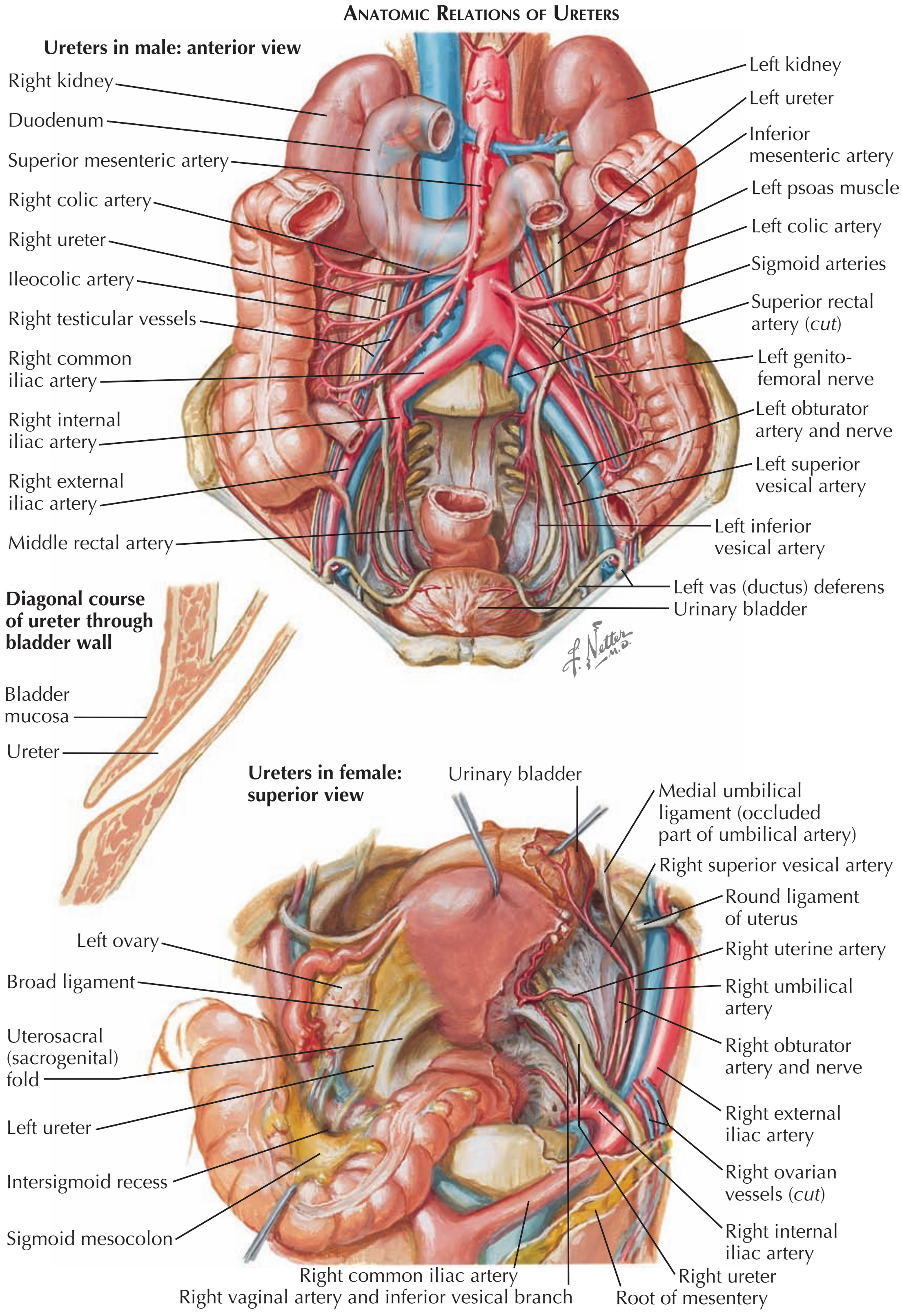
The kidneys, suprarenal glands, and perinephric fat are all contained within a condensed, membranous layer of renal fascia. The renal fascia consists of a stronger posterior and more delicate anterior layer, previously described as two separate structures (posterior fascia of Zuckerkandl and anterior fascia of Gerota) that fused laterally to form the lateral conal fascia. At present, however, the renal fascia is regarded as a single structure.

The posterior layer originates from the lateral aspect of the psoas fascia, fusing variably with the anterior layer of thoracolumbar fascia (quadratus lumborum fascia) and transversalis fascia as it passes posterior and lateral to the kidney. It then wraps around the anterior aspect of the kidneys as the anterior layer. The medial continuation of the anterior layer ensheaths the renal vessels and fuses with the sheaths of the abdominal aorta and inferior vena cava. In some individuals, these fusions are very delicate and may rupture under pressure, permitting midline crossing of accumulated fluid. Another delicate fascial prolongation extends inferomedially along each ureter as periureteric fascia.

There is substantial disagreement over the craniocaudal boundaries of the renal fascia, reflecting its tenuous and elusive structure. In their cranial aspect, the anterior and posterior layers are generally thought to fuse superior to the suprarenal glands. In several studies this fused fascia appears to define a closed space on each side, which is then continuous with the diaphragmatic fascia in the region of the coronary ligament on the right and the gastrophrenic ligament on the left. Other studies, however, have challenged the notion that these spaces are closed, finding the perinephric space to be continuous with the bare area between liver and diaphragm on the right and the subphrenic extraperitoneal space on the left.

Caudally, fusion of the anterior and posterior layers is incomplete, which allows perinephric fluid to seep into the iliac fossa of the greater pelvis. Likewise, air injected into the presacral space is known to reach the perinephric space through this same opening; this technique was formerly used to visualize the kidneys in a procedure known as retroperitoneal pneumography.

External to the renal fascia lies the retroperitoneal paranephric fat (pararenal fat body), a continuation of the extraperitoneal fat. The perinephric and paranephric fat are both traversed by variably developed strands of collagenous connective tissue that extend from the renal fascia, which may cause them to appear multilaminate in sectional studies.



ANATOMIC RELATIONS OF URETERS

Ureters in male: anterior view
Right kidney
Duodenum
Superior mesenteric artery
Right colic artery
Right ureter
Ileocolic artery
Right testicular vessels
Right common iliac artery
Right internal iliac artery
Right external iliac artery
Middle rectal artery
Left kidney
Left ureter
Inferior mesenteric artery
Left psoas muscle
Left colic artery
Sigmoid arteries
Superior rectal artery (cut)
Left genito-femoral nerve
Left obturator artery and nerve
Left superior vesical artery
Left inferior vesical artery
Left vas (ductus) deferens
Urinary bladder
F. Netter M.D.
Diagonal course of ureter through bladder wall
Bladder mucosa
Ureter
Ureters in female: superior view
Urinary bladder
Medial umbilical ligament (occluded part of umbilical artery)
Right superior vesical artery
Round ligament of uterus
Right uterine artery
Right umbilical artery
Right obturator artery and nerve
Right external iliac artery
Right ovarian vessels (cut)
Right internal iliac artery
Right ureter
Root of mesentery
Right common iliac artery
Right vaginal artery and inferior vesical branch
Left ovary
Broad ligament
Uterosacral (sacrogenital) fold
Left ureter
Intersigmoid recess
Sigmoid mesocolon

URETERS: POSITION, RELATIONS, GROSS STRUCTURE

The ureters are paired muscular ducts that convey urine from the kidneys to the bladder. Each ureter begins medial to the ipsilateral kidney as a continuation of the renal pelvis and ends upon insertion into the posterior bladder wall. The ureters are retroperitoneal for their entire length, which is approximately 30 cm.

The ureters vary in diameter from 2 to 8 mm, increasing in size in the lower lumbar area. They are generally narrowest at their origin from the renal pelvis, at the crossing of the pelvic rim, and at their termination as they traverse the bladder wall. As a result, renal stones (see Plate 6-3) most often become impacted within or proximal to these three sites.

ABDOMINAL PORTION

As the ureters exit the kidneys, they pass anterior to the psoas muscles and genitofemoral nerves. In addition, the right ureter lies posterior to the second (descending) part of the duodenum. More inferiorly, near their entry into the greater (false) pelvis, both ureters pass posterior to the gonadal vessels.

The ureters also cross the unpaired vessels supplying the intestines. The left ureter passes posterior to the left colic and sigmoid vessels, while the right ureter passes posterior to the right colic, ileocolic, and terminal superior mesenteric vessels. These vessels are contained within the fusion fascia formed as the ascending and descending portions of the colon became secondarily retroperitoneal. Thus they do not have ureteric branches and can be easily mobilized along with the colon to access the ureters.

As the ureters enter the lesser (true) pelvis, they pass anterior to the sacroiliac joint and common iliac vessels.

PELVIC PORTION

The ureters enter the lesser pelvis anterior to the internal iliac arteries. As they descend along the posterolateral pelvic wall, they run medial to the obturator vessels/nerves and the superior vesical (umbilical) arteries. At the level of the ischial spines, the ureters turn medially alongside branches of the hypogastric bundle of nerves (see Plate 1-14). The other anatomic relationships in the pelvic region differ between the two genders.

Male. Just before the entering the bladder, each ureter passes inferior to the ipsilateral ductus (vas) deferens. At this point the ureters lie superior and anterior to the seminal glands (vesicles).

Female. As the ureters descend along the lateral walls of the lesser (true) pelvis, they course posterior and then parallel to the ovarian vessels contained in the suspensory ligaments of the ovary. The ureters pass medial to the origins of the uterine arteries from the internal iliac arteries. As the ureters turn anteromedially from the pelvic wall, they run anterior and parallel to the uterosacral fold, posterior and inferior to the ovaries. As they traverse the base of the broad ligament, about 1.5 cm lateral to the uterine cervix, the ureters pass inferior to the uterine arteries as the arteries course medially toward the uterus.

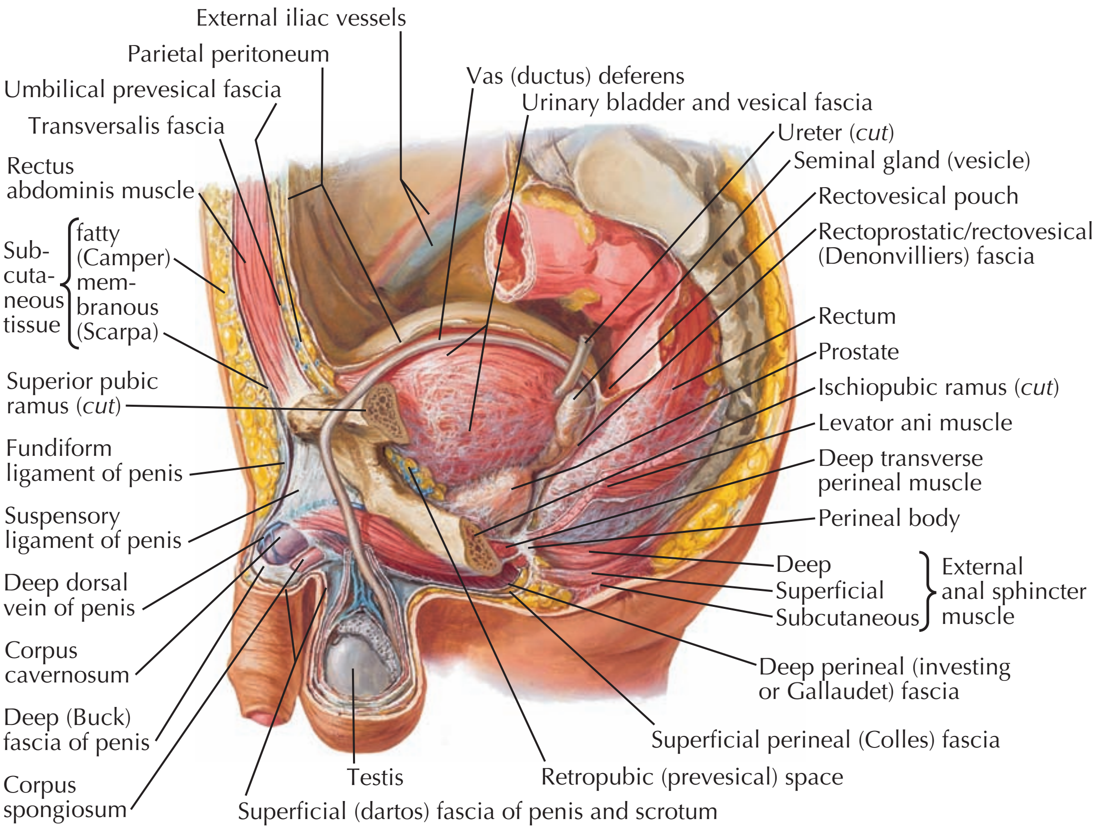
BLADDER INSERTION

The ureters penetrate the thick wall of the bladder about 2.5 cm from the midline. They run in an anteromedial direction within the wall of the bladder and then terminate at the ureteric orifices, which are 2 cm apart in the nondistended bladder. As intravesicular pressure increases, the intramural portions of the ureters become compressed, preventing reflux of urine. In this distended state, the ureteric orifices spread to become 5 cm apart.

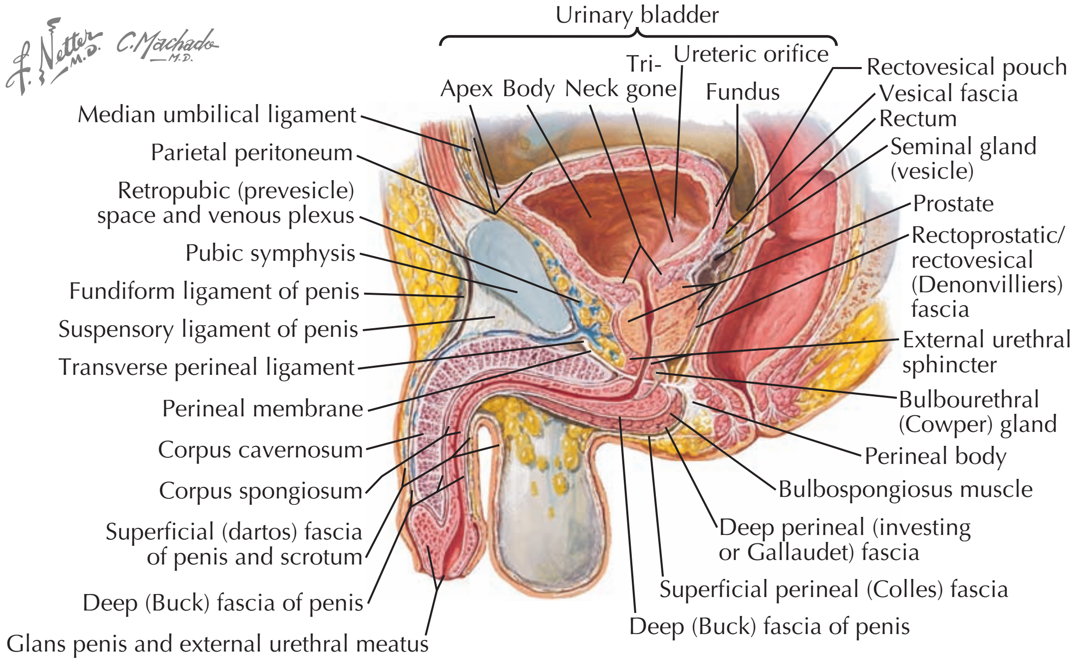
BLADDER: POSITION, RELATIONS, GROSS STRUCTURE

POSITION AND RELATIONS OF URINARY BLADDER: MALE

Paramedian (sagittal) dissection


External iliac vessels
Parietal peritoneum
Umbilical prevesical fascia
Transversalis fascia
Rectus abdominis muscle
Sub-cutaneous tissue
fatty (Camper)
membranous (Scarpa)
Superior pubic ramus (cut)
Fundiform ligament of penis
Suspensory ligament of penis
Deep dorsal vein of penis
Corpus cavernosum
Deep (Buck) fascia of penis
Corpus spongiosum
Superficial (dartos) fascia of penis and scrotum
Testis
Retropubic (prevesical) space
Superficial perineal (Colles) fascia
Deep perineal (investing or Gallaudet) fascia
Deep
Superficial
Subcutaneous
External anal sphincter muscle
Perineal body
Deep transverse perineal muscle
Levator ani muscle
Ischiopubic ramus (cut)
Prostate
Rectum
Rectoprostatic/rectovesical (Denonvilliers) fascia
Rectovesical pouch
Seminal gland (vesicle)
Ureter (cut)
Urinary bladder and vesical fascia
Vas (ductus) deferens

Median (sagittal) section


F. Netter M.D.
C.Machado M.D.
Urinary bladder
Apex
Body
Neck
Trigone
Ureteric orifice
Fundus
Median umbilical ligament
Parietal peritoneum
Retropubic (prevesicle) space and venous plexus
Pubic symphysis
Fundiform ligament of penis
Suspensory ligament of penis
Transverse perineal ligament
Perineal membrane
Corpus cavernosum
Corpus spongiosum
Superficial (dartos) fascia of penis and scrotum
Deep (Buck) fascia of penis
Glans penis and external urethral meatus
Rectovesical pouch
Vesical fascia
Rectum
Seminal gland (vesicle)
Prostate
Rectoprostatic/rectovesical (Denonvilliers) fascia
External urethral sphincter
Bulbourethral (Cowper) gland
Perineal body
Bulbospongiosus muscle
Deep perineal (investing or Gallaudet) fascia
Superficial perineal (Colles) fascia
Deep (Buck) fascia of penis

The urinary bladder is an expandable reservoir that receives urine from the ureters. When empty, the bladder lies entirely within the lesser pelvis and resembles a flattened, four-sided pyramid with rounded edges. The apex, which corresponds to the tip of the pyramid, is directed anteriorly. Opposite the apex is the base (fundus), the expansive posterior surface. Between the apex and fundus is the body of the bladder, which has a single superior surface, as well as two convex inferolateral surfaces separated by a rounded inferior edge. The bladder's most inferior and most fixed aspect is known as the neck. It is located just proximal to the outlet, also known as the internal urethral orifice.

The bladder wall consists of a loose, outer connective tissue layer, known as the vesical fascia; a three-layered muscularis propria of smooth muscle, known as the detrusor; and an internal mucosa. The ureters enter the bladder on its posteroinferior surface and then take an oblique course through its wall before terminating at the ureteric orifices. The two ureteric orifices, combined with the internal urethral orifice, bound an internal triangular region known as the trigone.

ANATOMIC RELATIONS

Anterior. The anterior portion of the bladder rests on the pubic symphysis and adjacent bodies of the pubic bones; when empty, the bladder rarely extends beyond their superior margin. Between the pubic bones/symphysis and the bladder is the retropubic (prevesical) space (of Retzius), which contains a matrix of loose areolar tissue encasing the anterior portions of the vesical and prostatic venous plexuses. This space facilitates extraperitoneal access to the bladder and prostate via suprapubic abdominal incision.

As the bladder fills with urine, the body expands, causing its anterosuperior aspect to ascend into the extraperitoneal space superior to the pubic crest. The base and neck of the bladder, in contrast, remain relatively constant in both shape and position.

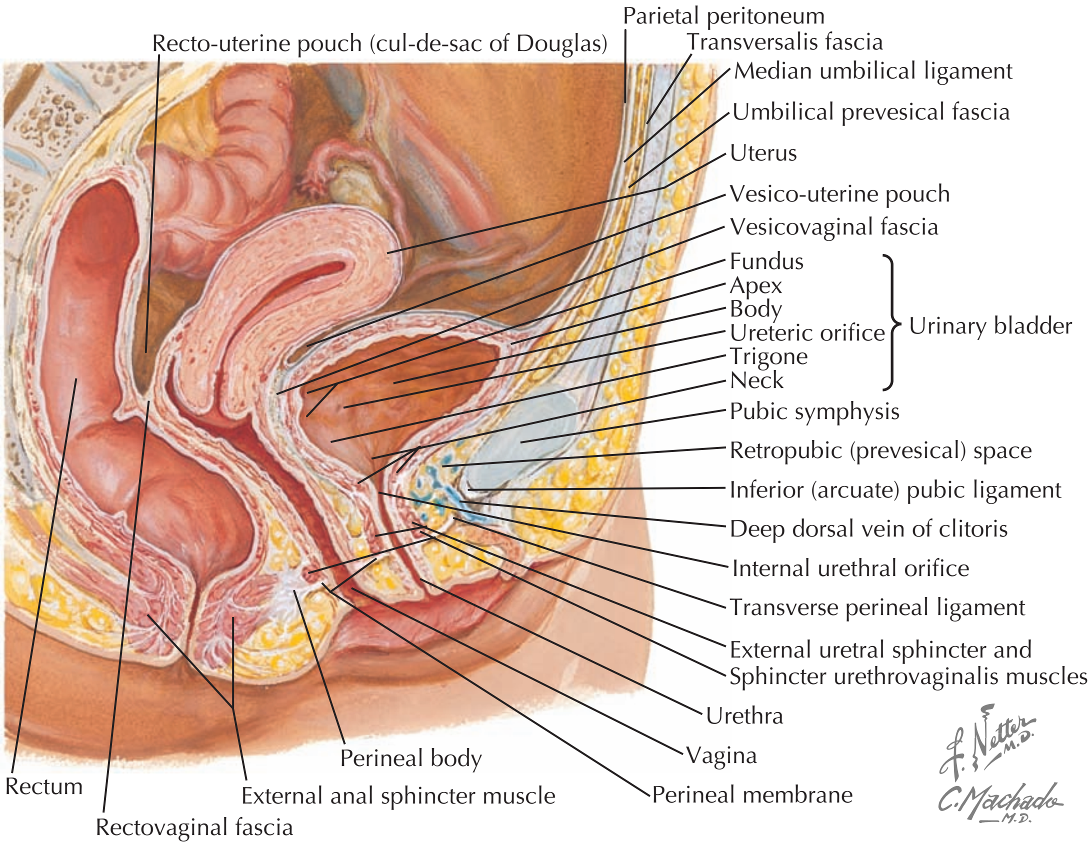
The apex of the empty bladder sends a solid, slender projection known as the median umbilical ligament superiorly along the midline of the abdominal wall, toward the umbilicus. This ligament represents a vestige of the urachus (see Plate 2-33) and rarely possesses a residual allantoic lumen. If a lumen is present, it infrequently may communicate with that of the bladder, but a urachus that is patent from bladder to the umbilicus is very rare.

Superior. The peritoneum covering the anterosuperior aspect of the bladder reflects onto the abdominal wall to form the paired supravesical fossae of the peritoneal cavity. These fossae are divided by the median umbilical ligament and bounded laterally by the obliterated umbilical arteries, which form the medial umbilical ligaments. The level of the supravesical fossae (and consequently, the superior extent of the retropubic space) changes with bladder emptying and filling.

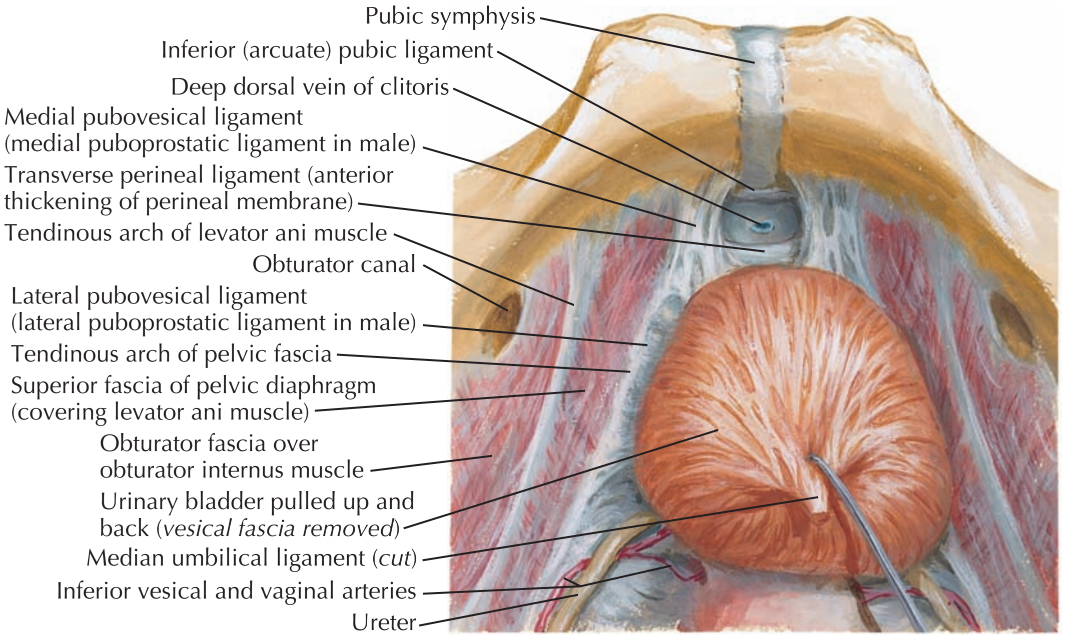
Lateral. The walls of the bladder are covered by peritoneum to the level of the umbilical artery/medial umbilical ligament. The reflection of the peritoneum from the lateral walls of the bladder onto the lateral

Position and Relations of Urinary Bladder: Female

Median (sagittal) section


Parietal peritoneum
Recto-uterine pouch (cul-de-sac of Douglas)
Transversalis fascia
Median umbilical ligament
Umbilical prevesical fascia
Uterus
Vesico-uterine pouch
Vesicovaginal fascia
Fundus
Apex
Body
Ureteric orifice
Trigone
Neck
Urinary bladder
Pubic symphysis
Retropubic (prevesical) space
Inferior (arcuate) pubic ligament
Deep dorsal vein of clitoris
Internal urethral orifice
Transverse perineal ligament
External uretral sphincter and
Sphincter urethrovaginalis muscles
Urethra
Vagina
Perineal membrane
Perineal body
External anal sphincter muscle
Rectum
Rectovaginal fascia
F. Netter M.D.
C. Machado M.D.

Superior view with peritoneum and vesical fascia removed


Pubic symphysis
Inferior (arcuate) pubic ligament
Deep dorsal vein of clitoris
Medial pubovesical ligament
(medial puboprostatic ligament in male)
Transverse perineal ligament (anterior
thickening of perineal membrane)
Tendinous arch of levator ani muscle
Obturator canal
Lateral pubovesical ligament
(lateral puboprostatic ligament in male)
Tendinous arch of pelvic fascia
Superior fascia of pelvic diaphragm
(covering levator ani muscle)
Obturator fascia over
obturator internus muscle
Urinary bladder pulled up and
back (*vesical fascia removed*)
Median umbilical ligament (*cut*)
Inferior vesical and vaginal arteries
Ureter

BLADDER: POSITION, RELATIONS, GROSS STRUCTURE *(Continued)*

pelvic walls forms the shallow paravesical fossae of the peritoneal cavity. These fossae extend posteriorly to the vasa deferentia in males. In females, they extend to the anterior aspect of the broad ligament, which conveys the round ligaments of the uterus. Inferior to the paravesical fossae, the loose areolar tissue of the retropubic space continues laterally.

Posterior. In the male, the two seminal glands (vesicles) and ampullae of the vasa deferentia lie between the base of the bladder and the rectum on each side of the midline. These structures are separated from the rectum by the rectoprostatic (rectovesical) fascia cor septum (also known as Denonvilliers fascia). This fascia is continuous with the tough envelopes of the ampullae of the vasa deferentia and seminal glands (vesicles), and it continues posterior to the prostate until it reaches the perineal body.

In the female, the urethra and bladder are separated from the vagina and cervix by the vesicovaginal fascia, which normally contains a small amount of areolar tissue. The vesicovaginal fascia, as well as the rectovaginal fascia (or septum, located posterior to the vagina), together are homologous to the male rectoprostatic (rectovesical) fascia.

In males, the rectoprostatic (rectovesical) fascia is located inferior to the rectovesical pouch, the inferiormost extent of the peritoneal cavity. In the fetus, this pouch is a deeper excavation, which dips posterior to the prostate as far as the pelvic floor. In females, the rectovaginal fascia is directly inferior to a similar space, termed the recto-uterine pouch (cul-de-sac of Douglas).

In the male, the peritoneum extends from the bladder around each side of the rectum toward the sacrum as a pair of sickle-shaped shelves called the sacrogenital (vesicosacral) folds, bounding the pararectal fossae. In the female, the sacrogenital (uterosacral) folds arise from the dorsolateral walls of the uterine cervix (see Plate 1-6). At the base of the bladder, these folds contain the terminal portions of the ureters and, in the male, the ductus deferens.

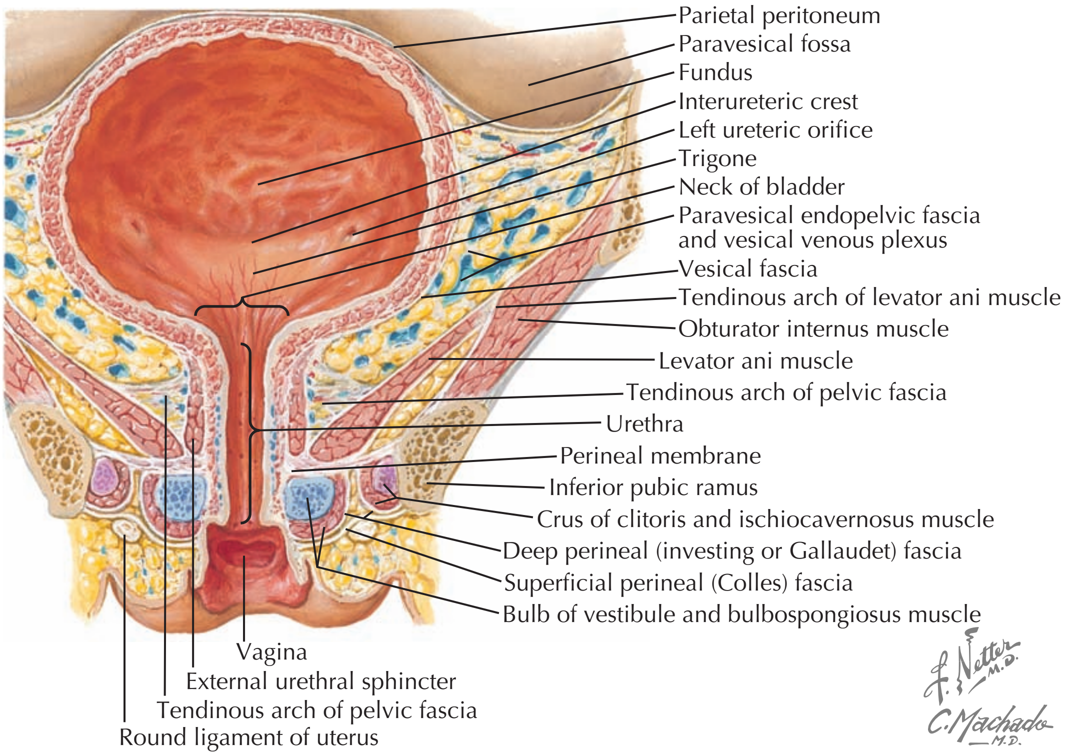
Inferior. Except for a variable layer of endopelvic fascia, the neck of the bladder rests directly on the pelvic floor muscles (e.g., levator ani) in females, whereas in males the prostate gland is interposed between them. In the male, the internal urethral orifice lies about 1 or 2 cm superior to, and 2 cm posterior to, the subpubic angle. In the female, the position of the urethral orifice is slightly more inferior. In the newborn, the bladder is more abdominal than pelvic in position, and the urethral orifice may be situated as far superiorly as the pubic crest.

LIGAMENTOUS ATTACHMENTS

The inferior, subperitoneal aspect of the bladder is connected to the pubis by two ligaments originating in the prostatic fascia in males and vesical fascia in females.

Coronal Cross-Sections of Urinary Bladder

Female: frontal section


Parietal peritoneum
Paravesical fossa
Fundus
Interureteric crest
Left ureteric orifice
Trigone
Neck of bladder
Paravesical endopelvic fascia and vesical venous plexus
Vesical fascia
Tendinous arch of levator ani muscle
Obturator internus muscle
Levator ani muscle
Tendinous arch of pelvic fascia
Urethra
Perineal membrane
Inferior pubic ramus
Crus of clitoris and ischiocavernosus muscle
Deep perineal (investing or Gallaudet) fascia
Superficial perineal (Colles) fascia
Bulb of vestibule and bulbospongiosus muscle
Vagina
External urethral sphincter
Tendinous arch of pelvic fascia
Round ligament of uterus
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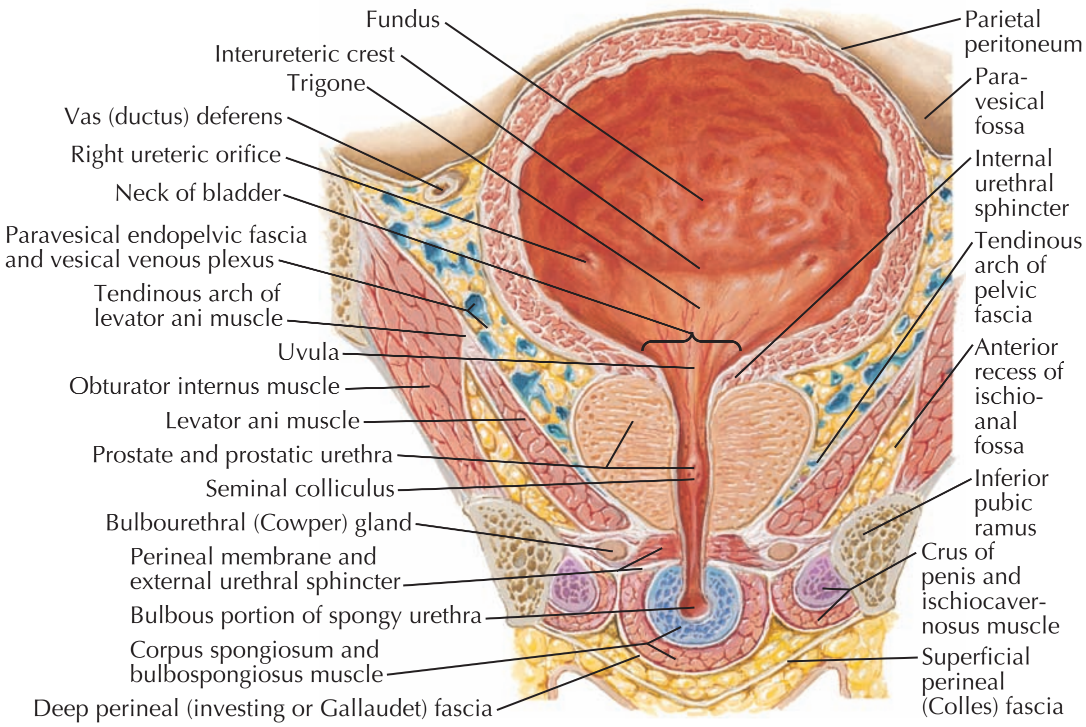
Male: frontal section


Fundus
Interureteric crest
Trigone
Vas (ductus) deferens
Right ureteric orifice
Neck of bladder
Paravesical endopelvic fascia and vesical venous plexus
Tendinous arch of levator ani muscle
Uvula
Obturator internus muscle
Levator ani muscle
Prostate and prostatic urethra
Seminal colliculus
Bulbourethral (Cowper) gland
Perineal membrane and external urethral sphincter
Bulbous portion of spongy urethra
Corpus spongiosum and bulbospongiosus muscle
Deep perineal (investing or Gallaudet) fascia
Parietal peritoneum
Paravesical fossa
Internal urethral sphincter
Tendinous arch of pelvic fascia
Anterior recess of ischioanal fossa
Inferior pubic ramus
Crus of penis and ischiocavernosus muscle
Superficial perineal (Colles) fascia

Bladder: Position, Relations, Gross Structure *(Continued)*

The first of these ligaments is known as the medial puboprostatic ligament in males and the medial pubovesical ligament in females. This ligament lies close to the pelvic floor and flanks the deep dorsal vein of the penis (or clitoris) as it pierces up the pelvic floor to enter the prostatic (or vesical) venous plexus. Other ligaments flanking this vein include the inferior (arcuate) pubic ligament anteriorly, which forms the inferior margin of the pubic symphysis, and the transverse perineal ligament posteriorly, which is an anterior thickening of the perineal membrane.

The second ligament is known as the lateral puboprostatic ligament in males and the lateral pubovesical ligament in females. This ligament is formed by a lateral extension of the prostatic (or, in females, vesical) fascia over the inferior group of vesical arteries, pudendal veins (draining the vesical plexus), and autonomic nerves. The terminal part of the ureter and (in males) vas deferens contribute adventitia to this ligament. At its lateral edge, this ligament joins the superior fascia of the pelvic diaphragm, which invests the levator ani. This linear area of attachment is known as the tendinous arch of the pelvic fascia.

BLADDER STRUCTURE

The detrusor muscle, which contracts under parasympathetic stimulation, consists of three layers of muscle. Unlike in the gastrointestinal tract, however, these muscle layers are not clearly distinct in all areas.

The outer muscle layer consists of predominantly longitudinal fibers, which are especially numerous in the midline region and near the neck. The thin middle muscle layer encircles the fundus and body. In males, additional circular fibers create the internal urethral sphincter in the inferior neck, which contracts during sympathetically stimulated ejaculation to prevent reflux of semen into the bladder.

The innermost layer of the detrusor contains additional longitudinal fibers. In the region of the trigone, this layer is intimately attached to the mucosa and forms the trigonal muscle.

Around the ureteric orifices, the muscular coat of each ureter also fans out into the bladder. Some of these muscle fibers cross the midline to unite with strands from the opposite side, raising an interureteric crest.

The sides of the trigone are outlined by yet another group of submucosal fibers, known as Bell muscle, which connect the ureteral muscles with the wall of the urethra. Tension across these bands, especially when combined with pressure from the neighboring middle lobe of the prostate (in males), leads to a small elevation above the bladder neck known as the uvula.

The innermost layer of the bladder is the mucosa. When the bladder is empty, the mucosa is corrugated by numerous folds. As the bladder distends, however, the folds are obliterated. The mucosa of the trigone is anatomically distinct, however, because it is firmly attached to the muscularis, consequently appearing smooth even when the bladder is empty.

RENAL VASCULATURE

RENAL ARTERIES

At rest, 20% to 25% of the cardiac output circulates through the kidneys. Accordingly, the renal arteries are major paired branches of the abdominal aorta. These arteries arise from the abdominal aorta roughly at the level of the L1/L2 intervertebral disc, about 1 cm inferior to the origin of the superior mesenteric artery.

Because the aorta is slightly to the left of the midline here, the left renal artery is shorter than the right. It takes a nearly horizontal course to the left kidney.

Because the right kidney is positioned slightly inferior to the left kidney, the right renal artery arises either inferior to the origin of the left or, more frequently, takes an oblique path. During its course, the right renal artery passes posterior to the inferior vena cava.

Both renal arteries run posterior and slightly cranial to the corresponding renal veins. The arteries are surrounded by a dense plexus of nerve fibers that arrive by way of the celiac, superior mesenteric, and aorticorenal ganglia, located adjacent to the origins of the celiac, superior mesenteric, and renal arteries.

Anterior Relations. On the left, the body of the pancreas lies anterior or slightly superior to the left renal artery, with the splenic vein between them. The inferior mesenteric vein may or may not be in close relationship with the left renal vessels, depending on where it joins the splenic vein.

On the right, the duodenum and the head of the pancreas are adherent to the anterior surface of the right renal artery (see Plate 1-1 for a picture of these relationships).

Posterior Relations. On the left, the left diaphragmatic crus, psoas muscle, ascending lumbar vein (the lateral root of the hemiazygos vein), and sympathetic trunk lie posterior to the renal artery.

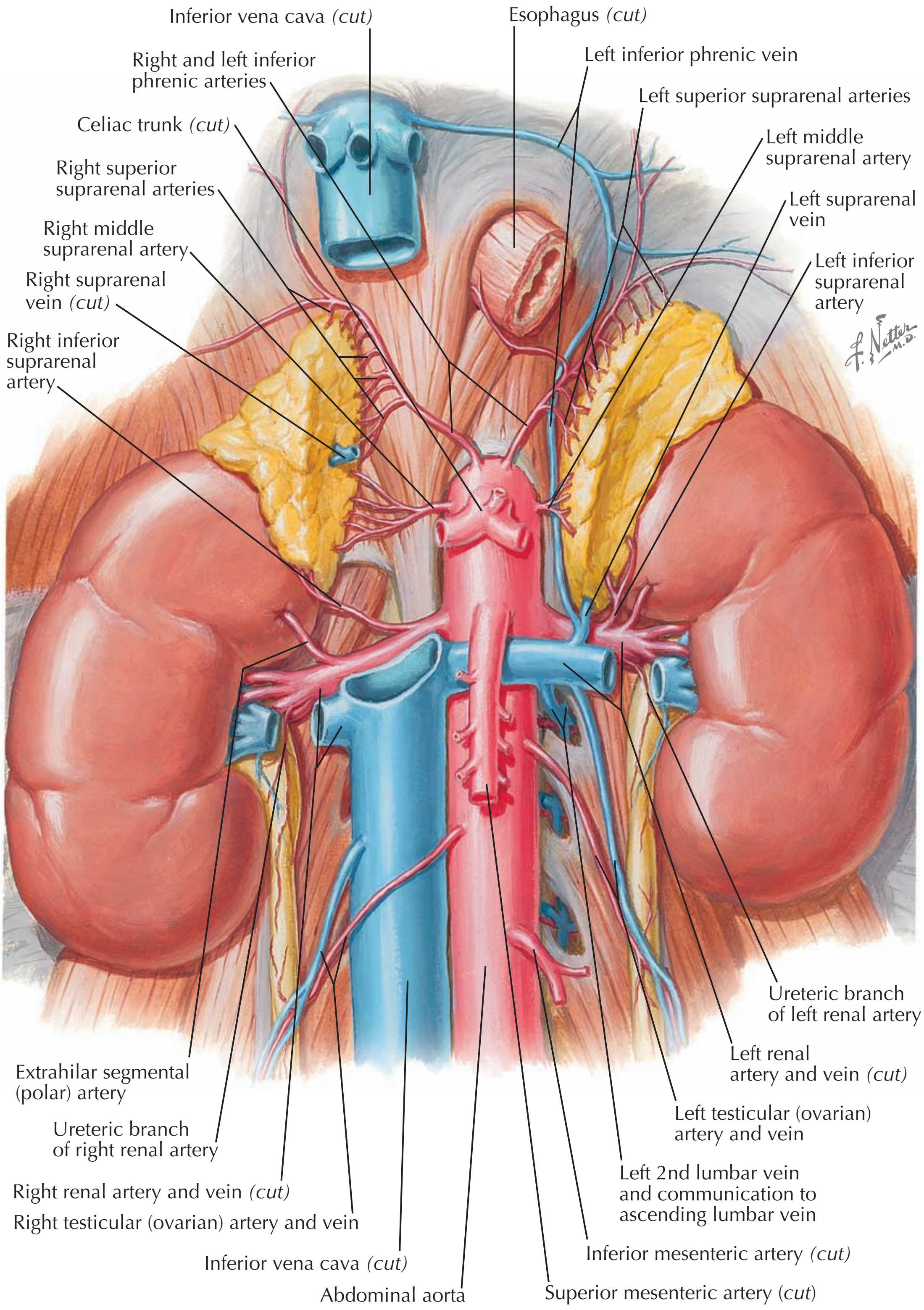
On the right, the azygos vein, right lumbar lymphatic trunk, and right crus of the diaphragm lie posterior to the proximal section of the renal artery. The psoas muscle lies posterior to the middle section of the renal artery.

Presegmental Branches. Each renal artery sends slender inferior suprarenal arteries to the ipsilateral suprarenal gland. The suprarenal glands also receive middle and superior suprarenal arteries, which are branches of the aorta and the inferior phrenic arteries, respectively.

Each renal artery, as well as its segmental branches near the hilum, also supplies numerous small branches to the perinephric fat, renal fascia, renal capsule, renal pelvis, and ureter.

Segmental Branches. Near the hilum, each renal artery splits into a small posterior and a larger anterior branch. These major branches, in turn, give rise to segmental arteries, each destined for one of the kidney's wedge-shaped vascular segments. In most kidneys, three to five segmental arteries supply the parenchyma in a characteristic pattern.

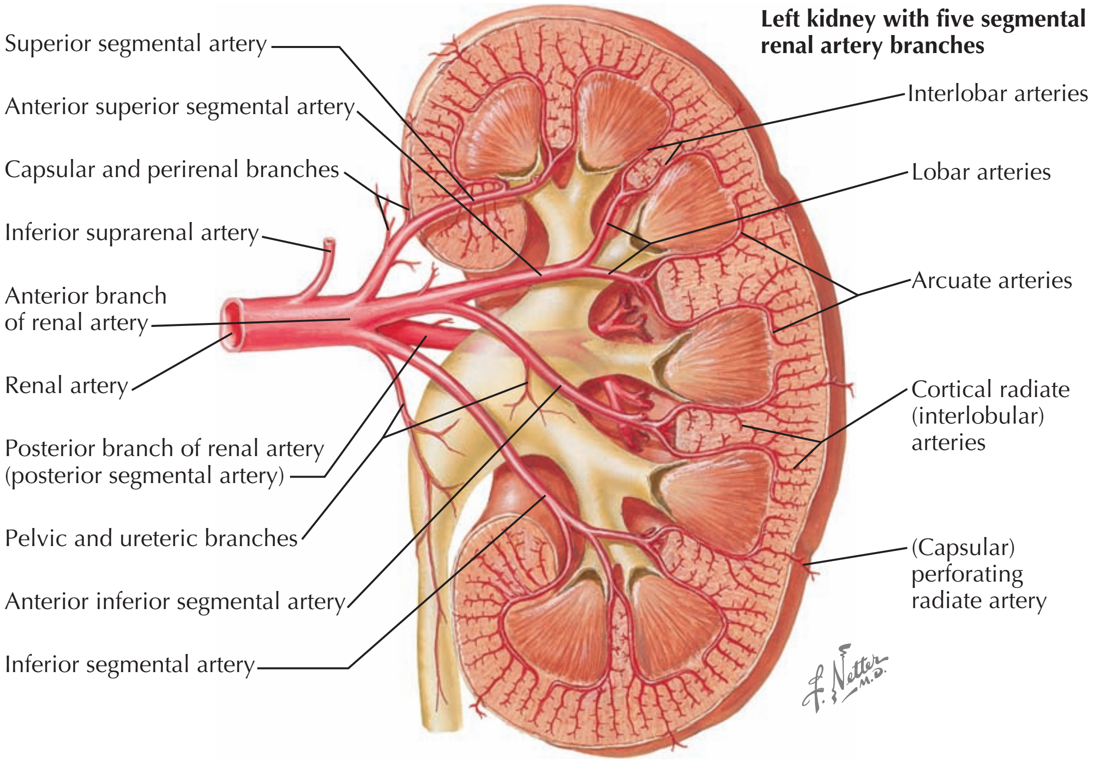
RENAL ARTERY AND VEIN IN SITU


Inferior vena cava (cut)
Esophagus (cut)
Right and left inferior phrenic arteries
Left inferior phrenic vein
Left superior suprarenal arteries
Celiac trunk (cut)
Left middle suprarenal artery
Right superior suprarenal arteries
Left suprarenal vein
Right middle suprarenal artery
Left inferior suprarenal artery
Right suprarenal vein (cut)
Right inferior suprarenal artery
Ureteric branch of left renal artery
Left renal artery and vein (cut)
Extrahilar segmental (polar) artery
Left testicular (ovarian) artery and vein
Ureteric branch of right renal artery
Left 2nd lumbar vein and communication to ascending lumbar vein
Right renal artery and vein (cut)
Right testicular (ovarian) artery and vein
Inferior mesenteric artery (cut)
Inferior vena cava (cut)
Abdominal aorta
Superior mesenteric artery (cut)

Most of the time, the posterior branch continues as the single posterior segmental artery, which runs posterior to the renal pelvis. The anterior branch, in contrast, courses farther into the sinus before dividing into two to four anterior segmental arteries, which enter the parenchyma between the veins and the renal pelvis.

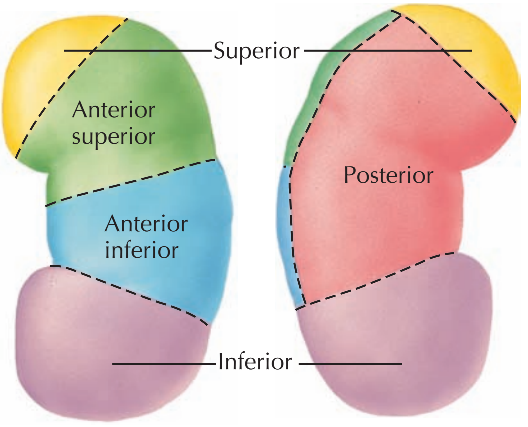
Each segmental artery supplies a vascular renal segment, a distinct portion of the kidney named for the segmental artery it receives. In kidneys with five segmental vessels, a characteristic pattern has been identified. The superior and inferior segments, located at the poles, receive the superior and inferior segmental arteries from the anterior branch of the renal artery. On the anterior surface, the area between the poles is divided into the anterior superior and anterior inferior segments; these receive the anterior superior and anterior inferior segmental arteries from the anterior branch of the renal artery. On the posterior surface, a single posterior segment lies between the polar segments and

RENAL ARTERY SEGMENTAL BRANCHES AND INTRARENAL ARTERIES


Left kidney with five segmental renal artery branches
Superior segmental artery
Anterior superior segmental artery
Capsular and perirenal branches
Inferior suprarenal artery
Anterior branch of renal artery
Renal artery
Posterior branch of renal artery (posterior segmental artery)
Pelvic and ureteric branches
Anterior inferior segmental artery
Inferior segmental artery
Interlobar arteries
Lobar arteries
Arcuate arteries
Cortical radiate (interlobular) arteries
(Capsular) perforating radiate artery
F. Netter M.D.

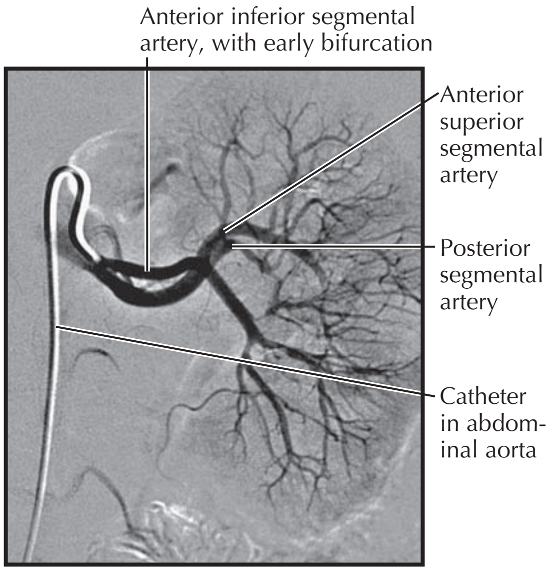
For simplicity, arcuate branches of arcuate arteries are not depicted. Most cortical radiate arteries arise from arcuate branches, but some arise directly from both arcuate and interlobar arteries, as shown here.

Vascular renal segments (five branch pattern)


Superior
Anterior superior
Anterior inferior
Posterior
Inferior

Anterior surface of left kidney

Posterior surface of left kidney


Anterior inferior segmental artery, with early bifurcation
Anterior superior segmental artery
Posterior segmental artery
Catheter in abdominal aorta

Digital subtraction angiography of a left kidney with three segmental renal artery branches, as well as an early bifurcation.

RENAL VASCULATURE *(Continued)*

receives the posterior segmental artery. The terminology is easily adjusted for kidneys with fewer than five segmental arteries/vascular segments via comparison with the five segment pattern. The superior or posterior segmental arteries/segments are most likely to be absent.

Segmental arteries do not anastomose with one another. Therefore, occlusion or injury to a segmental branch will cause segmental renal ischemia.

The border between the posterior and the two anterior segments follows an intersegmental line (of Brödel), which runs along the lateral edge of the kidney on the posterior surface. No major vascular channels are likely to run beneath this line, which makes it a preferred area for nephrotomy incisions. The area, however, is by no means bloodless because segmental boundaries are not planar; rather, they are jagged, as small vessels of adjacent segments interdigitate along borders.

Intrarenal Arteries. Segmental arteries branch into lobar arteries, each of which supplies a renal pyramid or group of pyramids sharing a common apex. Just before entering the parenchyma, lobar arteries divide into two or three interlobar arteries. Often, segmental arteries divide directly into interlobar arteries, skipping the intermediate order of branching. The interlobar arteries travel in the renal columns, near or alongside the pyramids, following a gently curving course toward the cortical arches.

As each interlobar artery approaches the base of the adjacent pyramid, it divides into several (four to six) arcuate arteries, which diverge at right angles, penetrating the cortical arch overlying the convex base of the pyramid. Although multiple arcuate arteries participate in supplying the arch overlying each pyramid, arcuate arteries generally do not anastomose with one another.

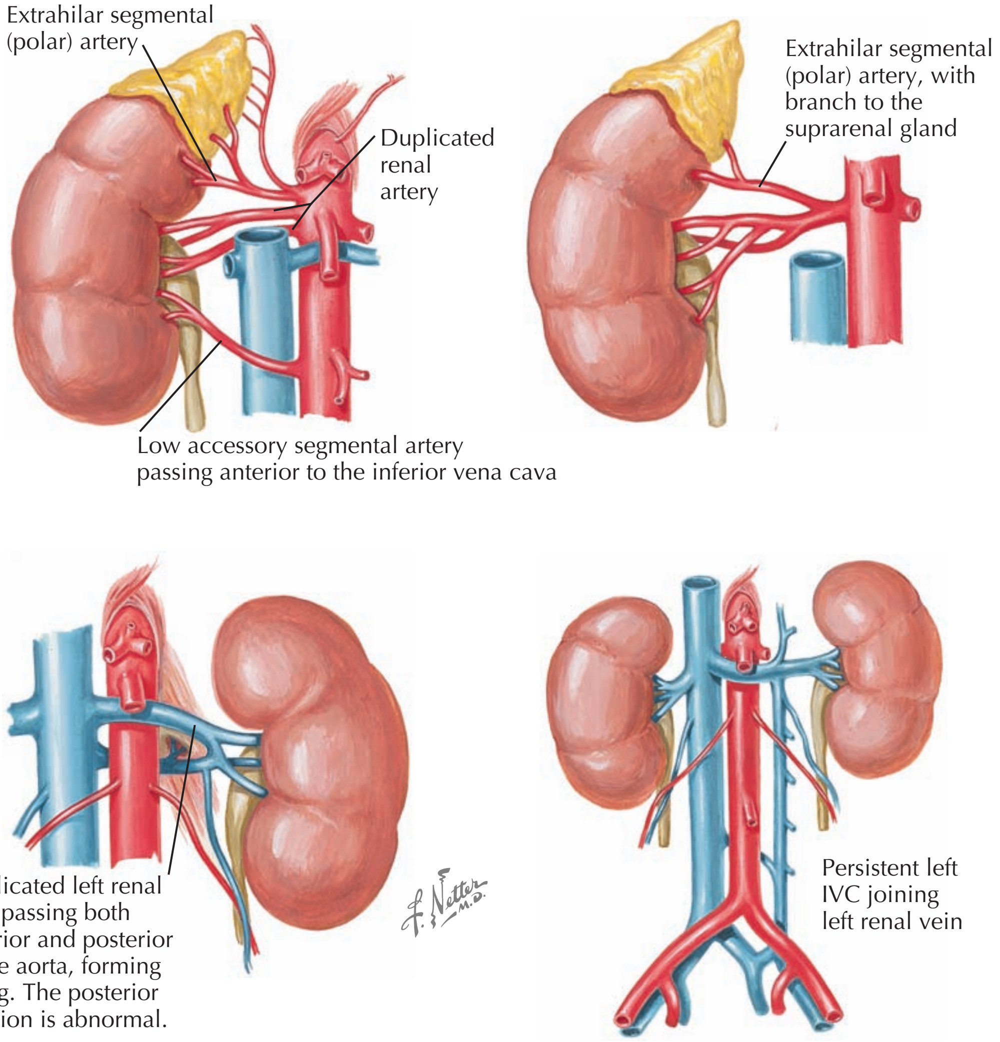
Arcuate arteries branch in turn (although for simplicity, this order of branching is usually omitted from two-dimensional illustrations) and these arcuate branches give rise to cortical radiate (interlobular) arteries. Although most cortical radiate arteries arise from arcuate branches, some arise directly from arcuate or interlobar arteries. Some cortical radiate arteries extend into the renal columns, whereas others extend through the arches. The chief purpose of the cortical radiate arteries is to provide afferent arterioles to the glomeruli (see Plate 1-19). Some of the arteries extending through the arches, however, may reach or pass through the fibrous capsule as perforating arteries, often establishing small connections with extracapsular vessels.

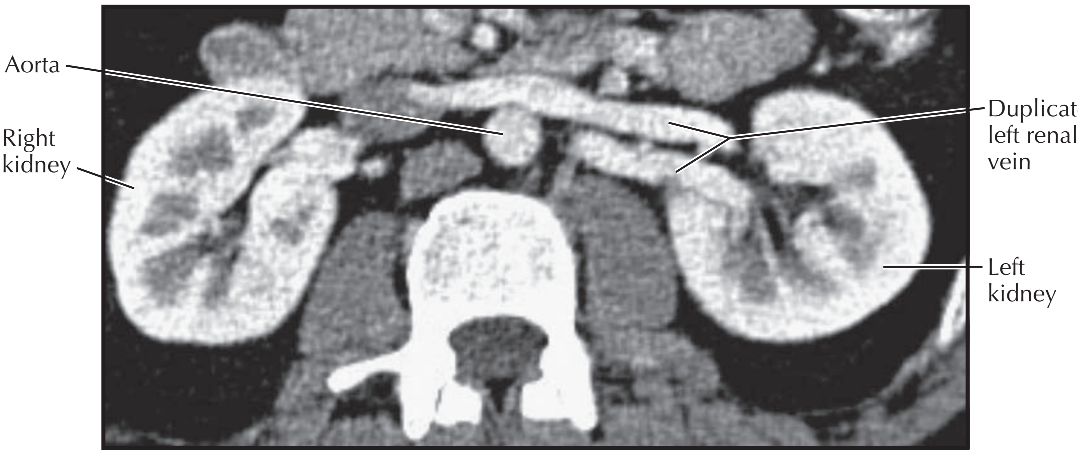
Spiral arteries arise from interlobar arteries in the renal columns, running a more tortuous course as they turn back (recur) toward the renal sinus to supply the neighboring portion of the renal calyces and send branches into the apical aspect of the adjacent pyramid.

Anomalies of the Renal Artery. In about two thirds of individuals, a single renal artery passes to each kidney. In the remainder, a variety of anomalies may be seen.

Roughly 1 in 10 kidneys, for example, receives additional branches from the aorta that enter at the hilum, known as accessory or supernumerary renal arteries. Accessory arteries are not duplicated vessels, but rather one or more segmental (end) arteries uniquely responsible for a portion of the kidney. Accessory arteries are regarded as persistent embryonic lateral splanchnic arteries. They may arise from the aorta as high as the diaphragm or as low as the internal iliac artery; however, they most frequently arise caudal to the main artery. Most occur on the left side. Right accessory arteries arising caudal to the main artery usually pass anterior to the inferior vena cava (IVC).

VARIATIONS IN RENAL ARTERY AND VEIN


Extrahilar segmental (polar) artery
Duplicated renal artery
Extrahilar segmental (polar) artery, with branch to the suprarenal gland
Low accessory segmental artery passing anterior to the inferior vena cava
Duplicated left renal vein passing both anterior and posterior to the aorta, forming a ring. The posterior position is abnormal.
F. Netter M.D.
Persistent left IVC joining left renal vein


Aorta
Right kidney
Duplicated left renal vein
Left kidney

Computed tomography (contrast-enhanced) of duplicated left renal vein

RENAL VASCULATURE *(Continued)*

Up to one in four kidneys receives an extrahilar segmental (polar) artery that passes directly to the superior or inferior pole; half of these arise directly from the aorta, and half arise as an early (proximal or prehilar) segmental branch of the main renal artery. Accessory inferior polar arteries crossing anterior to the ureter can either cause or aggravate ureteric obstructions.

Finally, the renal arteries may give rise to branches normally derived from other vessels, such as the inferior phrenic, middle suprarenal, gonadal, pancreatic, or colic arteries, as well as one or more of the lumbar arteries.

RENAL VEINS

The venous branches draining the renal parenchyma converge within the renal sinus and, upon leaving the hilum, unite to form the renal vein. The renal veins run anterior and slightly caudal to the renal arteries to enter the IVC.

Because the IVC lies on the right side of the vertebral column, the left renal vein is nearly three times longer than the right vein. Consequently, left kidneys are preferred as donor kidneys.

The left renal vein runs posterior to the splenic vein and body of the pancreas. It receives the left suprarenal vein and the left gonadal (testicular or ovarian) vein. It also connects with the hemiazygos vein by way of the ascending lumbar vein. It crosses the aorta anteriorly, below the origin of the superior mesenteric artery, and empties into the IVC at a level slightly superior to that of the right renal vein.

The right renal vein runs posterior to the upper second (descending) part of the duodenum and may contact the head of the pancreas. It occasionally assists in forming the azygos vein by means of a connecting branch. Unlike the left renal vein, however, the right renal vein does not receive the right gonadal or suprarenal veins, which instead connect directly to the inferior vena cava. The right renal vein joins the inferior vena cava after a very short course, usually of 2 to 2.5 cm, but sometimes 1 cm or less.

Unlike the arterial supply, the venous system is safeguarded by collaterals. These include anastomoses between renal veins, segmental veins, veins of the azygos system, inferior phrenic veins, and rarely, the splenic vein. The veins of the perinephric and paranephric fat and renal fascia connect the subcapsular intrarenal channels with veins draining the adjacent body walls.

Tributaries of the Renal Vein. Numerous small subcapsular veins are grouped in tiny radial arrays called stellate veins (see Plate 1-19). These communicate with capsular and perinephric veins, as well as with intrarenal veins. The stellate veins empty into the cortical radiate (interlobular) veins which, in turn, drain into the arcuate veins. The arcuate veins empty into the interlobar veins following the general arterial pattern. These intrinsic renal veins have extensive collaterals.

Eventually the veins unite into four to six trunks that converge within the renal sinus, lying anterior but only in a roughly similar pattern to the segmental arteries. Approximately 1 to 2 cm medial to the hilum, these trunks join to form the renal vein.

Anomalies of the Renal Vein. Unlike in other vascular beds, anomalies of the renal veins are far less common than those of the renal arteries. The major venous anomalies include duplicated or multiple renal veins. Duplicated veins are most common on the right side, where they may pass both anterior and posterior to the renal pelvis. When present on the left side, a duplicated vein often runs posterior to the aorta, so that the aorta is encircled by two renal veins. In a rarer anomaly, a persistent left inferior vena cava may join the left renal vein.

VASCULATURE OF URETERS AND BLADDER

URETERS

The blood supply of the ureters is variable and asymmetric. Indeed, any nearby arteries that are primarily retroperitoneal or subperitoneal may provide branches to the ureters.

In the abdomen, consistent ureteric branches arise from the renal arteries, which supply the ureters either directly or via a branch to the renal pelvis. Less consistent branches arise from the gonadal (testicular or ovarian) arteries, common and external iliac arteries, or aorta. These branches extend laterally to the abdominal ureter, which can thus undergo gentle medial traction during surgery.

In the pelvis, consistent ureteric branches arise from the uterine arteries in females and the inferior vesical arteries in males. Less consistent branches arise from the gonadal (testicular or ovarian), superior vesical, or internal iliac arteries. These branches extend medially to the pelvic ureter, which can thus undergo gentle lateral traction during surgery. In this region, the ureter is adherent to the posterior aspect of the serosa and thus also receives small twigs from minor peritoneal arteries.

As all of these branches reach the ureter, they divide into ascending and descending limbs that form longitudinal, anastomotic meshes on the outer ureter wall. These meshes usually establish functional collateral circulation; however, in approximately 10% to 15% of individuals, sufficient collaterals do not form. Furthermore, ureteric branches are small and relatively delicate. Thus disruption of these branches may lead to ischemia. During surgical procedures, the location, disposition, and arterial supply of the ureters must be carefully evaluated.

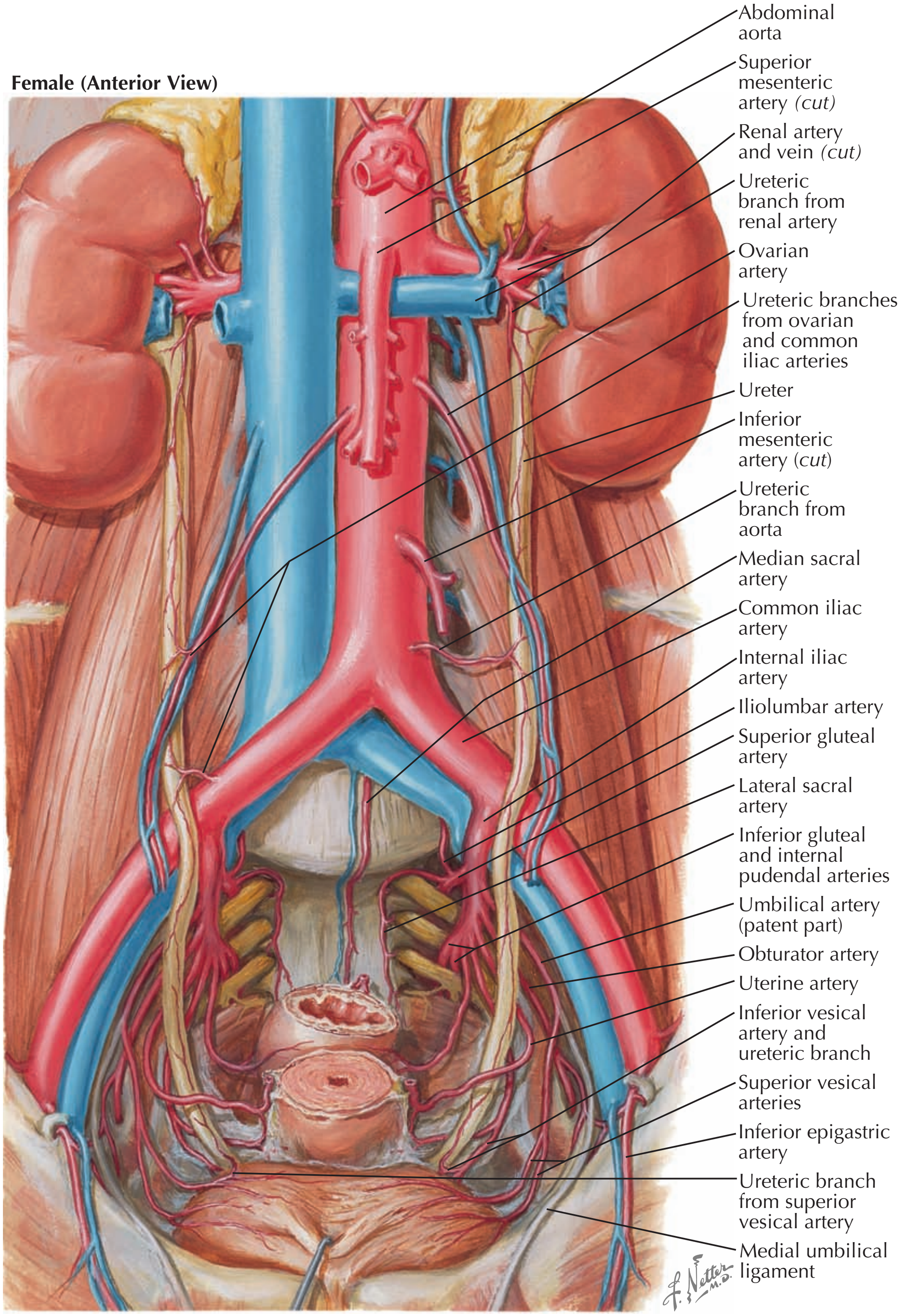
The distribution of ureteric veins follows that of the arteries. These vessels drain to the renal vein; the inferior vena cava and its tributaries; and the endopelvic venous plexuses.

URINARY BLADDER

The arterial supply to the urinary bladder arises from the fanlike ramification of the internal iliac vessels, usually from the anterior branches. Although the branching pattern of the internal iliac vessels is variable, the arteries that ultimately reach the bladder are quite consistent. In general, two main arteries (or groups of arteries) may be distinguished:

1. *The superior vesical arteries* each arise as one or more branches of the patent umbilical arteries, usually just below the level of the pelvic brim. Beyond the origin of these branches, the umbilical arteries obliterate after birth, forming the medial umbilical ligaments.

   The superior vesical arteries provide the most constant and significant blood supply to the bladder. The branches course over the body and fundus of the bladder. They anastomose with each other, with their contralateral fellows, and with branches of the inferior vesical arteries. Their dynamic tortuosity and overall length allow for the changes in bladder size that occur with filling and emptying. Superior vesical arteries may also give rise to ureteric branches and, in males, to the deferential arteries. In infants, a small urachal branch may extend toward the umbilicus, sometimes anastomosing with the inferior epigastric arteries.
2. *The inferior vesical arteries* may arise as independent branches of the internal iliac arteries, in common with the middle rectal arteries, or—commonly in females—from the uterine artery (directly or via vaginal branches).


Female (Anterior View)
Abdominal aorta
Superior mesenteric artery *(cut)*
Renal artery and vein *(cut)*
Ureteric branch from renal artery
Ovarian artery
Ureteric branches from ovarian and common iliac arteries
Ureter
Inferior mesenteric artery (*cut*)
Ureteric branch from aorta
Median sacral artery
Common iliac artery
Internal iliac artery
Iliolumbar artery
Superior gluteal artery
Lateral sacral artery
Inferior gluteal and internal pudendal arteries
Umbilical artery (patent part)
Obturator artery
Uterine artery
Inferior vesical artery and ureteric branch
Superior vesical arteries
Inferior epigastric artery
Ureteric branch from superior vesical artery
Medial umbilical ligament
F. Netter M.D.

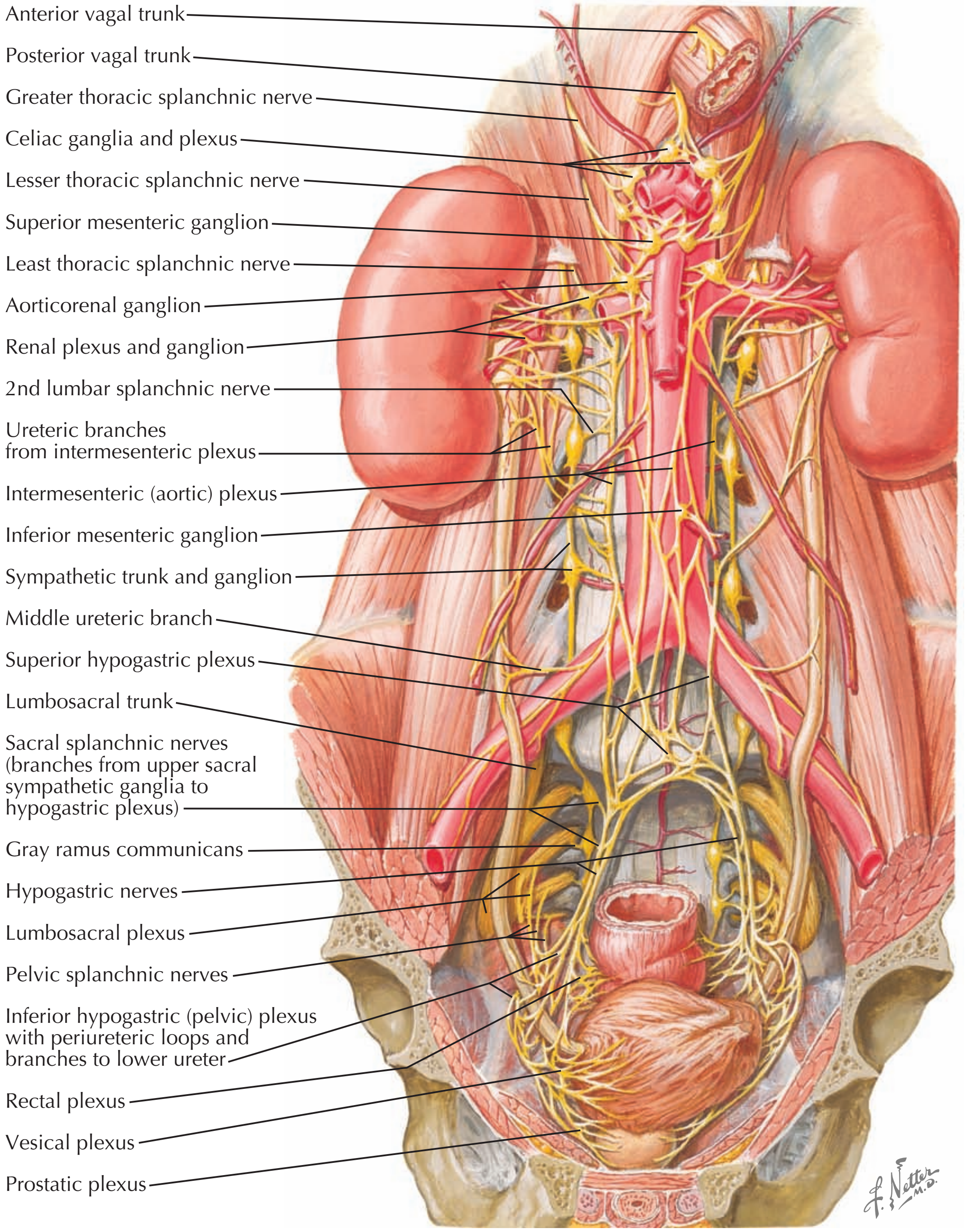
The inferior vesical arteries ramify over the fundus and neck of the bladder. On their way to the bladder, the arteries pass through the lateral ligaments of the bladder, where they usually give off ureteric branches and (in the male) branches to the seminal glands (vesicles) and prostate. In males, the inferior vesical arteries may give rise to the deferential arteries.

In some, the bladder receives additional branches from the obturator, inferior gluteal, or internal pudendal arteries.

Vesical veins are short, uniting into a rich vesical venous plexus around the base of the bladder. In males, this plexus is continuous with the prostatic venous plexus.

The vesical plexus (or prostatic plexus in males) communicates with the veins of the perineum, receiving the dorsal vein of the clitoris (or penis). Multiple interconnecting channels lead from the plexus to the internal iliac veins. Anastomoses with the parietal veins of the pelvis establish connections to the internal vertebral venous plexus, thighs, and gluteal regions.

INNERVATION OF KIDNEYS, URETERS AND BLADDER


Anterior vagal trunk
Posterior vagal trunk
Greater thoracic splanchnic nerve
Celiac ganglia and plexus
Lesser thoracic splanchnic nerve
Superior mesenteric ganglion
Least thoracic splanchnic nerve
Aorticorenal ganglion
Renal plexus and ganglion
2nd lumbar splanchnic nerve
Ureteric branches from intermesenteric plexus
Intermesenteric (aortic) plexus
Inferior mesenteric ganglion
Sympathetic trunk and ganglion
Middle ureteric branch
Superior hypogastric plexus
Lumbosacral trunk
Sacral splanchnic nerves (branches from upper sacral sympathetic ganglia to hypogastric plexus)
Gray ramus communicans
Hypogastric nerves
Lumbosacral plexus
Pelvic splanchnic nerves
Inferior hypogastric (pelvic) plexus with periureteric loops and branches to lower ureter
Rectal plexus
Vesical plexus
Prostatic plexus

INNERVATION OF URINARY SYSTEM

The urinary system receives a rich nerve supply from the autonomic nervous system, which is accompanied by visceral afferent nerve fibers. The autonomic nervous system facilitates bladder filling and stimulates emptying, whereas visceral afferent fibers from the bladder convey sensations produced by distention.

Once toilet training is complete, voiding can be consciously inhibited by somatic efferent fibers that stimulate contraction of the external urethral sphincter. Likewise voiding can be consciously enhanced by contraction of the diaphragm and abdominal wall muscles, which further compress the contracting bladder.

SYMPATHETIC

Anatomy. Sympathetic innervation of the urinary system begins in the lower thoracic and upper lumbar (T10-L2 or 3) spinal cord segments, where neurons of the intermediolateral (IML) cell column give rise to presynaptic (preganglionic) sympathetic fibers. These fibers exit the CNS via the anterior roots of the corresponding spinal nerves, traverse the initial parts of those spinal nerves, then exit via white rami communicans to reach the sympathetic trunks.

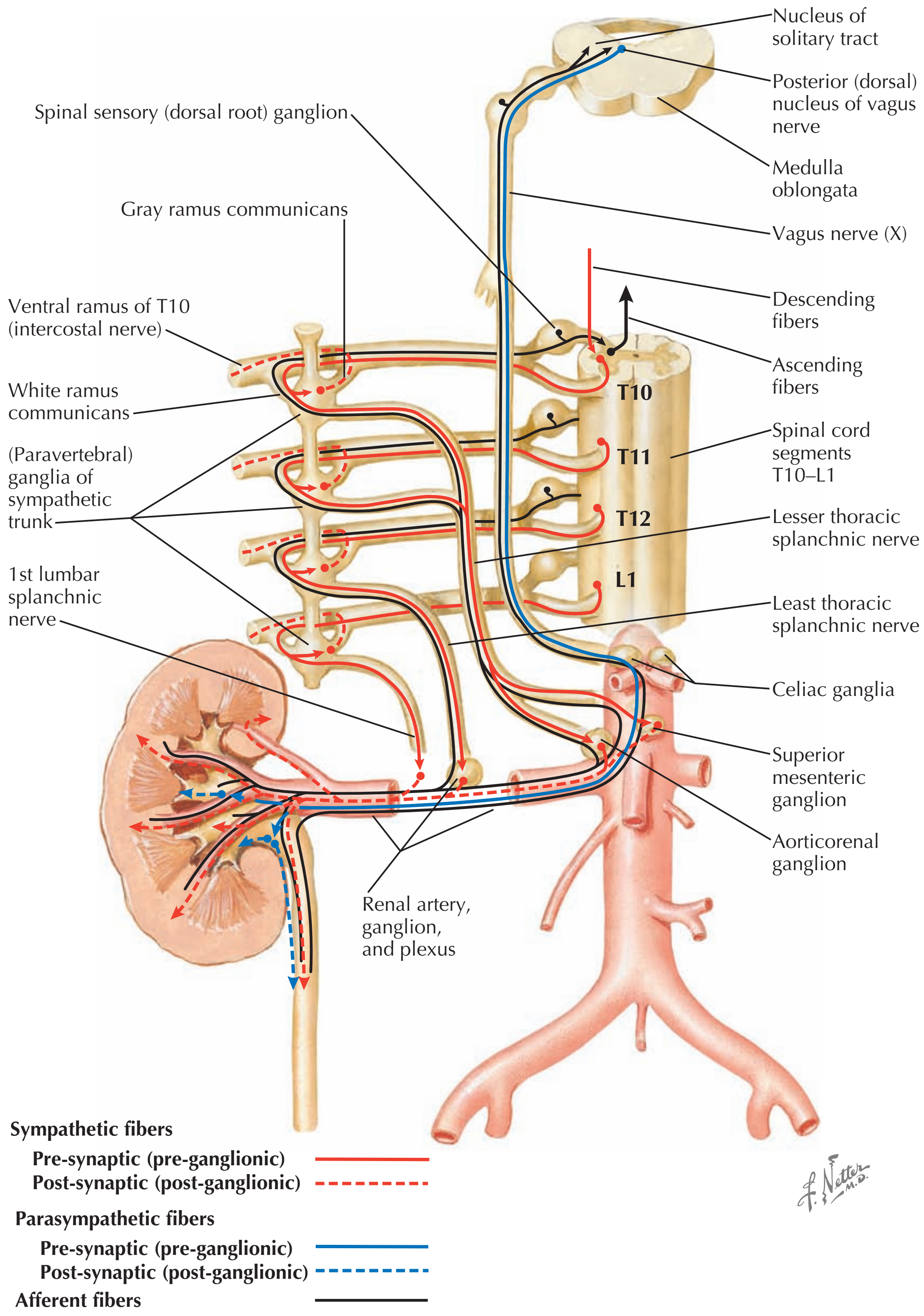
Within the sympathetic trunks, some fibers descend through the paravertebral ganglia to lower levels, but all of them leave the trunks, without synapsing, in visceral branches. These branches, also known as the abdominopelvic splanchnic nerves, extend from the medial aspects of the trunks. They include the lesser thoracic (T10-11), least thoracic (T12), lumbar, and possibly sacral splanchnic nerves. Together, these nerves convey presynaptic fibers to the prevertebral ganglia, such as the celiac and aorticorenal ganglia, located near the major branches of the abdominal aorta. The presynaptic neurons synapse in these ganglia with postsynaptic neurons.

The pathway of sympathetic innervation to the kidneys and upper ureter (see Plate 1-15) begins in presynaptic fibers originating in the T10-L1 levels of the IML. These fibers travel through splanchnic nerves to synapse with neurons of the superior mesenteric ganglion, aorticorenal ganglia, and the small ganglia in the periarterial renal plexuses. Postsynaptic fibers reach the kidney and upper ureter via periarterial plexuses and branches.

The pathway of sympathetic innervation to the remainder of the ureters and urinary bladder begins with presynaptic fibers originating in the T12-L2(3) levels of the IML. These fibers travel through lumbar (and possibly sacral) splanchnic nerves and then the intermesenteric (aortic) plexus, then synapse with neurons in the inferior mesenteric ganglion or small ganglia of the aortic/hypogastric plexuses. Postsynaptic fibers descend into the pelvis via aortic, hypogastric, and pelvic (vesical) plexuses to reach the ureters and bladder.

Function. In the kidney, sympathetic tone has numerous effects on both the vasculature and renal tubules. Adrenergic receptors are located throughout the renal cortex and outer stripe of the outer zone of the renal

INNERVATION PATHWAYS OF THE KIDNEYS AND UPPER URETER


Nucleus of solitary tract
Posterior (dorsal) nucleus of vagus nerve
Medulla oblongata
Spinal sensory (dorsal root) ganglion
Vagus nerve (X)
Gray ramus communicans
Descending fibers
Ascending fibers
Ventral ramus of T10 (intercostal nerve)
White ramus communicans
T10
T11
T12
L1
Spinal cord segments T10–L1
(Paravertebral) ganglia of sympathetic trunk
Lesser thoracic splanchnic nerve
1st lumbar splanchnic nerve
Least thoracic splanchnic nerve
Celiac ganglia
Superior mesenteric ganglion
Aorticorenal ganglion
Renal artery, ganglion, and plexus
Sympathetic fibers
Pre-synaptic (pre-ganglionic)
Post-synaptic (post-ganglionic)
Parasympathetic fibers
Pre-synaptic (pre-ganglionic)
Post-synaptic (post-ganglionic)
Afferent fibers
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INNERVATION OF URINARY SYSTEM *(Continued)*

medulla, with the greatest density in the juxtamedullary region of the inner cortex. Graded increases in renal sympathetic tone cause renin release from juxtaglomerular granular cells (see Plate 3-18), increase renal tubular sodium reabsorption, and decrease renal blood flow (by constricting afferent arterioles). These combined effects can contribute to the development and maintenance of hypertension. In experimental animals, for example, renal denervation is known to prevent or ameliorate hypertension. Likewise, in patients with drug-resistant essential hypertension, catheter-based radiofrequency renal denervation results in substantial and sustained reductions in systemic blood pressure.

Some renal sympathetic nerve fibers release dopamine, but there is no evidence that dopamine released during sympathetic stimulation affects renal function. Thus dopamine is not considered an endogenous neurotransmitter in the kidney. Likewise, despite the presence of acetylcholinesterase, renal sympathetic nerve stimulation is not affected by anticholinergic agents.

In the ureter, peristalsis is primarily myogenic in nature, driven by specialized pacemaker cells (see Plate 1-27). The efferent and afferent fibers of the extrinsic plexus, however, do appear to be involved in regulating the pacemaker cells.

In the bladder, activation of β-adrenergic receptors causes relaxation of the detrusor muscle, which facilitates bladder expansion during filling. Meanwhile, activation of α-adrenoceptors facilitates contraction of the trigone muscle. In males, trigonal muscle is circularly arranged to form an internal urethral sphincter, which prevents ejaculation into the bladder. As a result, stress may interfere with the ability to urinate by contracting this muscle. In females, in contrast, sphincteric arrangement of trigonal muscle is not evident.

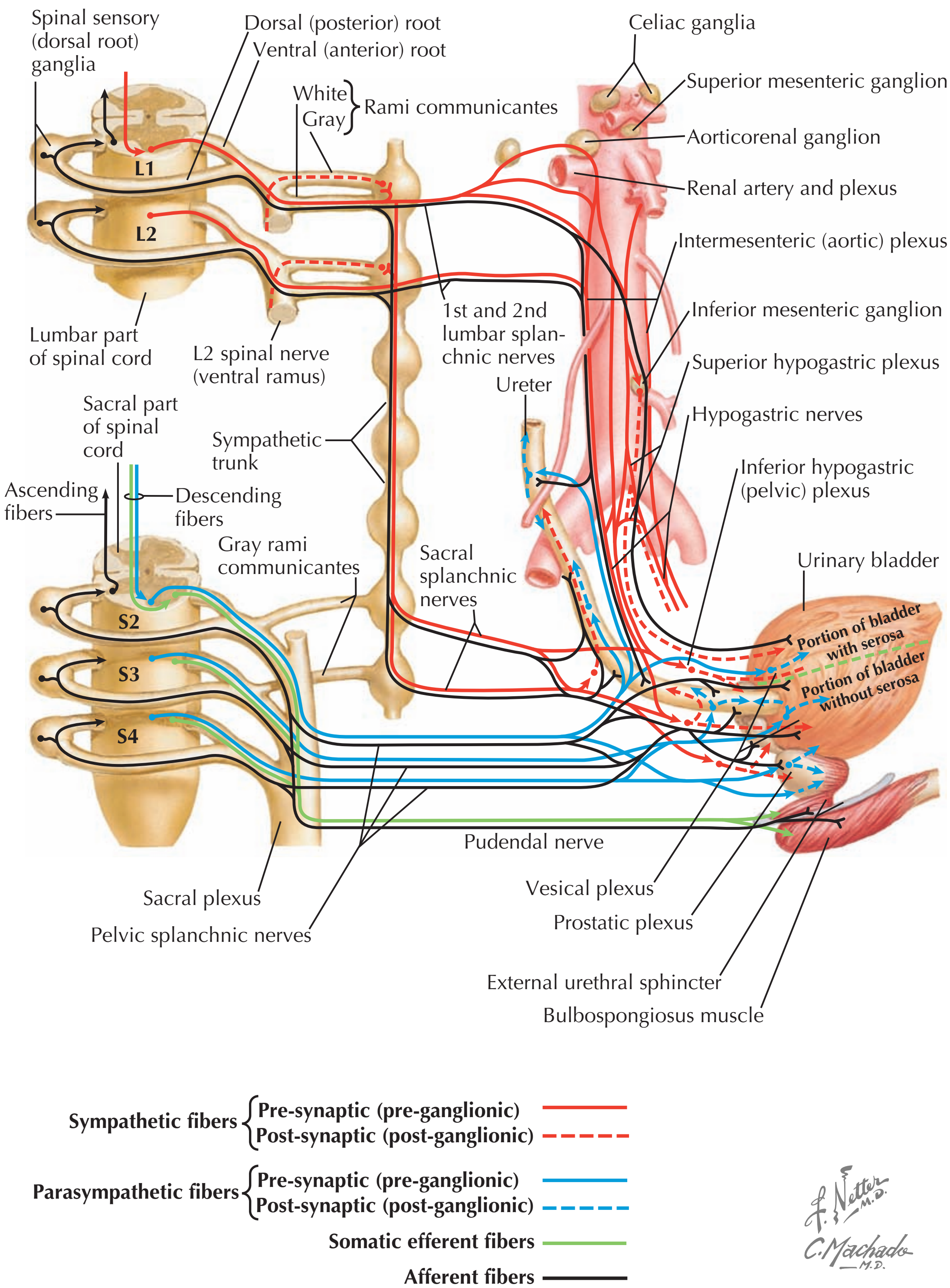
PARASYMPATHETIC

Anatomy. Parasympathetic innervation of the urinary system is derived from cranial and sacral sources. Both sources send presynaptic fibers all the way to the target organ, where they synapse with intrinsic (intramural) postsynaptic neurons.

The cranial source, which innervates the kidneys and upper ureters, is the vagus nerve; it conveys presynaptic fibers through the celiac and aorticorenal ganglia to the intrinsic renal and upper ureteric plexuses.

The sacral source, which innervates the remainder of the ureters and bladder, begins in the S2-S4 spinal cord segments, which contains neurons that give rise to

INNERVATION PATHWAYS OF THE URETER AND BLADDER


Spinal sensory (dorsal root) ganglia
Dorsal (posterior) root
Ventral (anterior) root
White
Gray
Rami communicantes
Celiac ganglia
Superior mesenteric ganglion
Aorticorenal ganglion
Renal artery and plexus
Intermesenteric (aortic) plexus
L1
L2
Lumbar part of spinal cord
L2 spinal nerve (ventral ramus)
1st and 2nd lumbar splanchnic nerves
Inferior mesenteric ganglion
Superior hypogastric plexus
Ureter
Sacral part of spinal cord
Sympathetic trunk
Hypogastric nerves
Ascending fibers
Descending fibers
Inferior hypogastric (pelvic) plexus
Gray rami communicantes
Sacral splanchnic nerves
Urinary bladder
S2
S3
S4
Portion of bladder with serosa
Portion of bladder without serosa
Pudendal nerve
Sacral plexus
Vesical plexus
Pelvic splanchnic nerves
Prostatic plexus
External urethral sphincter
Bulbospongiosus muscle
Sympathetic fibers
Pre-synaptic (pre-ganglionic)
Post-synaptic (post-ganglionic)
Parasympathetic fibers
Pre-synaptic (pre-ganglionic)
Post-synaptic (post-ganglionic)
Somatic efferent fibers
Afferent fibers
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C.Machado M.D.

INNERVATION OF URINARY SYSTEM *(Continued)*

presynaptic parasympathetic fibers. These fibers enter the initial portions of spinal nerves S2-S4 and then exit via pelvic splanchnic nerves, which convey them to the intrinsic plexuses of the ureters and bladder. Of note, the upper ureter may receive branches of these parasympathetic fibers, even though its primary source of parasympathetic innervation is the vagus nerve.

Function. In the kidney, the role of vagal (cholinergic) function is unclear. In the ureter, parasympathetic stimulation probably modulates intrinsic pacemaker cells.

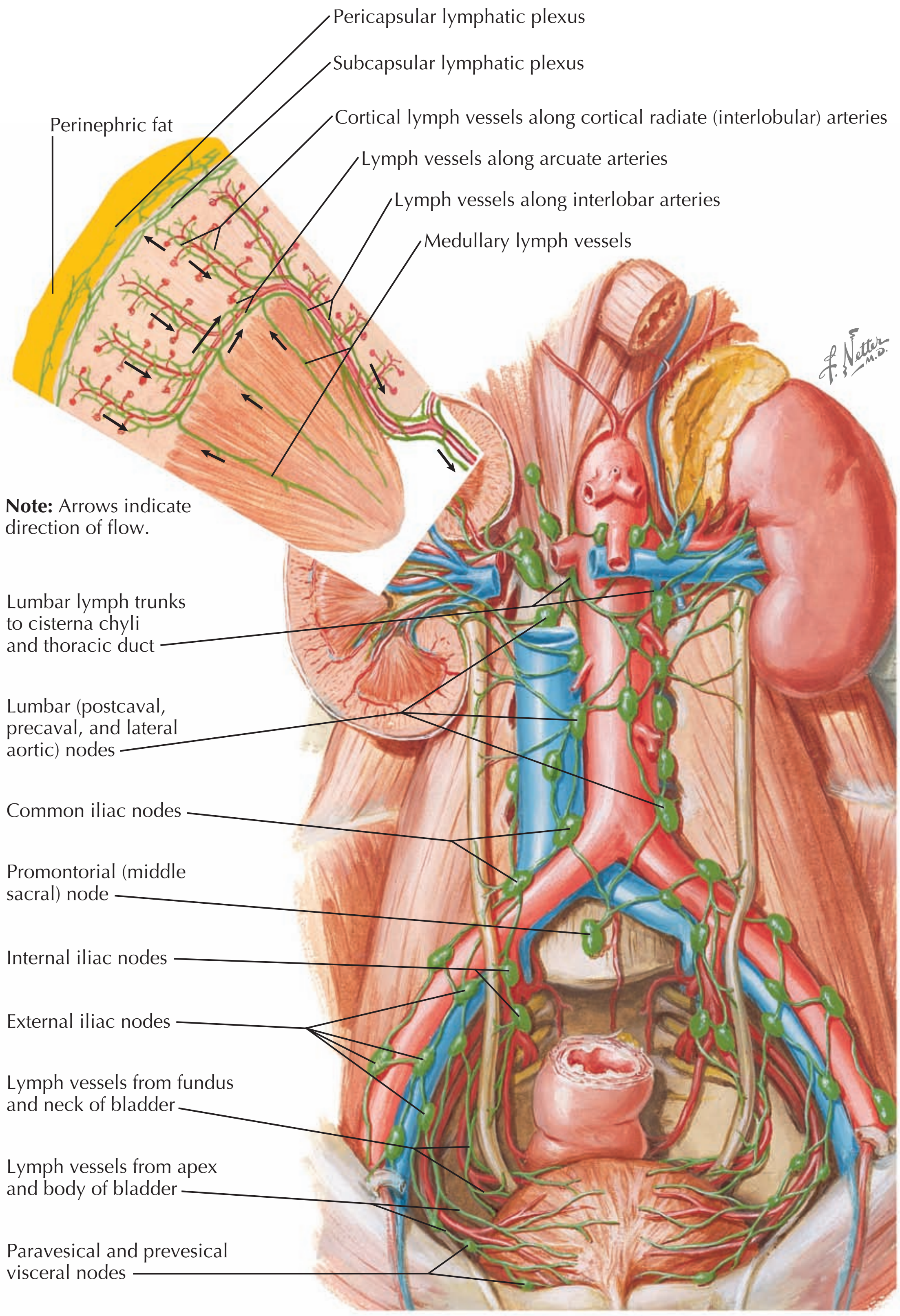
In the bladder, parasympathetic stimulation triggers contraction of the detrusor muscle and, by inhibiting sympathetic tone, also indirectly relaxes the trigonal muscle. In males, relaxation of the trigonal muscle includes relaxation of the internal urethral sphincter. The combination of detrusor contraction and sphincter relaxation enables micturition.

AFFERENT

Afferent innervation from the urinary system carries pain sensations and also plays a critical role in intrinsic reflexes. The pathways for pain sensation depend on whether the organ is invested with serosa. In those organs with serosa, such as the kidneys, abdominal ureters, and superior surface of the bladder, afferent pain fibers follow the pathways of sympathetic innervation in a retrograde direction until they reach spinal sensory ganglia. Referred pain from these organs is experienced at the dermatomes corresponding to the levels where the presynaptic fibers enter the sympathetic chain. The pain of pyelonephritis, or of an impacted stone in the renal pelvis or abdominal ureter, is experienced at levels T10-L1. The sensation of a distended bladder is experienced in T12-L2.

In contrast, afferent fibers conveying pain from organs without serosa (i.e., subperitoneal viscera, such as the neck of the bladder, terminal ureters, prostate, cervix, and upper vagina), as well as fibers involved in reflex arcs, generally follow the pathways of parasympathetic innervation in a retrograde direction until they reach cranial and sacral sensory ganglia. Thus, the visceral afferents conducting pain impulses from subperitoneal viscera have cell bodies located in the S2-S4 spinal sensory ganglia, with sensations perceived in the corresponding dermatomes. Mechanoreceptors and chemoreceptors that play a role in renorenal reflexes also send projections along vagal afferent fibers to vagal sensory ganglia. Likewise, the reflexive emptying of a moderately distended bladder, such as occurs in infants, is transacted at sacral levels.

LYMPHATICS OF URINARY SYSTEM


Pericapsular lymphatic plexus
Subcapsular lymphatic plexus
Perinephric fat
Cortical lymph vessels along cortical radiate (interlobular) arteries
Lymph vessels along arcuate arteries
Lymph vessels along interlobar arteries
Medullary lymph vessels
F. Netter M.D.
Lumbar lymph trunks to cisterna chyli and thoracic duct
Lumbar (postcaval, precaval, and lateral aortic) nodes
Common iliac nodes
Promontorial (middle sacral) node
Internal iliac nodes
External iliac nodes
Lymph vessels from fundus and neck of bladder
Lymph vessels from apex and body of bladder
Paravesical and prevesical visceral nodes

Note: Arrows indicate direction of flow.

LOWER URINARY TRACT

In both the bladder and ureters, lymph first drains into a submucous network of lymph capillaries. These capillaries drain into a plexus located outside of the muscular wall. This plexus, in turn, connects to vessels that lead to regional lymph nodes. The vessels contain valves, whereas the plexus and capillaries do not.

Bladder. The apex and body of the bladder drain into vessels that reach the external iliac nodes (some via prevesical and paravesical visceral nodes). The fundus and neck drain into vessels that reach the internal iliac nodes (some via postvesical visceral nodes).

Ureter. The pelvic portion of the ureter is drained by a few lymph vessels that reach the internal iliac nodes either directly or via efferent vessels from the bladder. The abdominal portion of the ureter has channels that drain into the external and common iliac nodes. Near the kidney, drainage is to the lumbar (caval and lateral aortic) nodes, either by direct communication or via renal lymphatic trunks.

KIDNEY

Extrarenal. Beneath the surface of the kidney, a scanty subcapsular plexus of lymph capillaries anastomoses, by means of perforating channels, with pericapsular vessels in the perinephric fat. These vessles eventually drain into superior lumbar nodes. The subcapsular plexus also communicates sparingly with lymphatics in the deeper layers of the parenchyma.

Intrarenal. In the parenchyma, lymph capillaries accompany the blood vessels and are found chiefly in the perivascular connective tissue. The lymph capillaries that surround arterioles are generally larger and more numerous than those that surround venules.

The great majority of intrarenal lymphatics occur in the cortical and corticomedullary zones. In the outer cortex most lymphatics are associated with subcapsular veins and renal tubules, whereas in the midcortex they are associated with cortical radiate (interlobular) arteries and veins, glomeruli, and tubules. In the corticomedullary zone, lymphatics pass between loops of Henle and collecting ducts. In the medulla, sparse lymphatic channels drain structures in the region of the vasa recta.

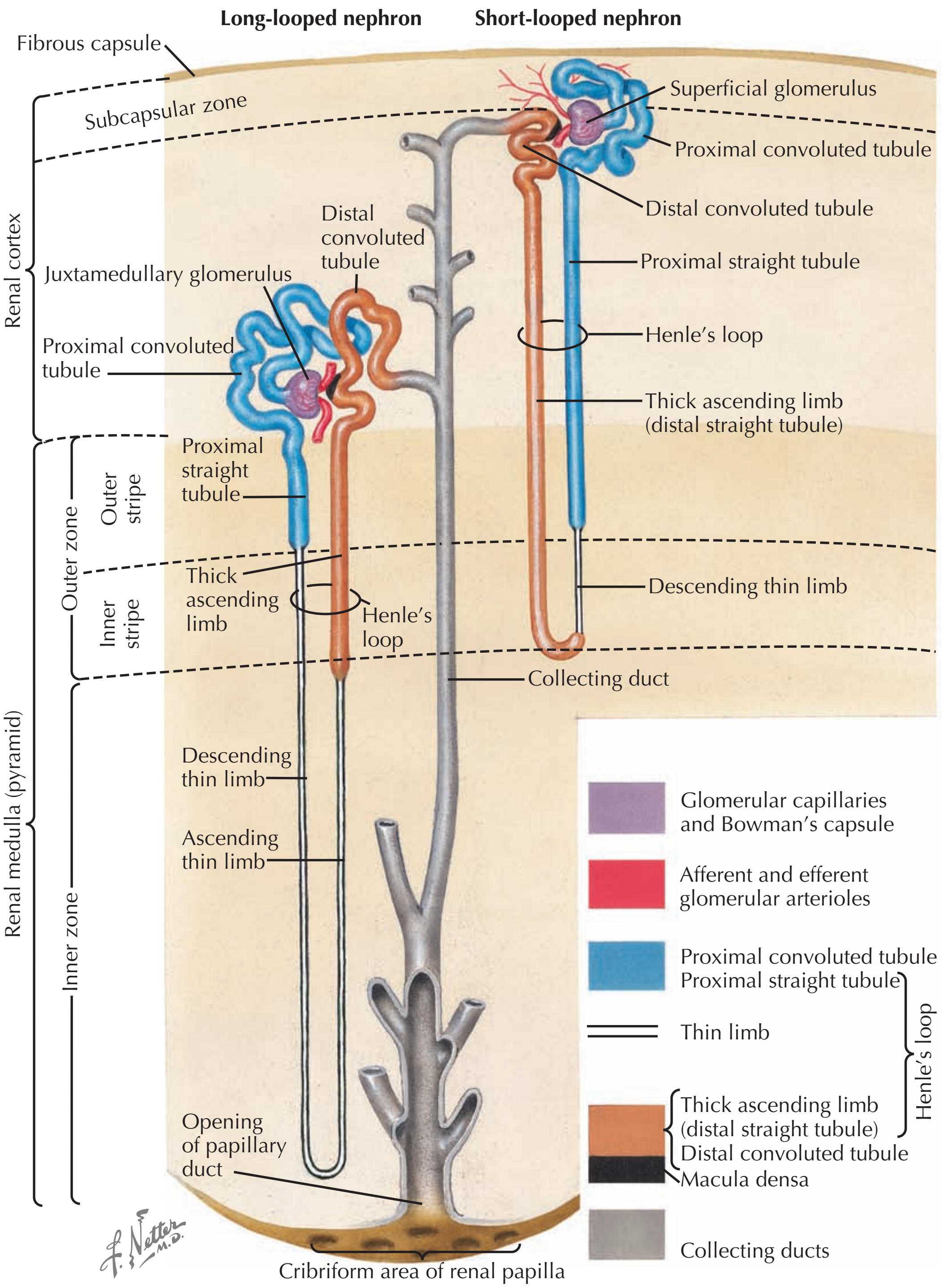
The lymph vessels exiting the parenchyma reach the renal sinus, often accompanying the arteries along the way, and form some four to five trunks that exit the hilum. They are joined by lymph vessels from the renal capsule and converge into a few valve-studded renal lymphatic trunks that accompany the renal vein. These trunks primarily drain to the superior lumbar nodes.

Except as a potential metastatic pathway, renal lymphatic drainage is commonly overlooked. The volume of lymph that drains from the kidney, however, is approximately 0.5 mL/min, thus approaching that of urine. Its primary function is probably to return reabsorbed protein to the blood. Some investigators have determined that the concentration of renin is greater in renal lymph than in renal vein plasma.

SUMMARY

The lymph drainage of the bladder and ureters passes to the external, internal, and common iliac groups of nodes—a sequential chain of nodes that drains next to the lumbar (caval/aortic) nodes. The lymph of the upper ureters and kidneys drains directly into the superior lumbar nodes. In both cases, lymph from the lumbar nodes ultimately flows to the thoracic duct via the lumbar lymph trunks.

OVERVIEW OF THE NEPHRON


Long-looped nephron
Short-looped nephron
Fibrous capsule
Subcapsular zone
Renal cortex
Superficial glomerulus
Proximal convoluted tubule
Distal convoluted tubule
Proximal straight tubule
Henle's loop
Thick ascending limb (distal straight tubule)
Descending thin limb
Collecting duct
Distal convoluted tubule
Juxtamedullary glomerulus
Proximal convoluted tubule
Proximal straight tubule
Outer stripe
Inner stripe
Outer zone
Thick ascending limb
Henle's loop
Renal medulla (pyramid)
Inner zone
Descending thin limb
Ascending thin limb
Opening of papillary duct
Cribriform area of renal papilla
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Glomerular capillaries and Bowman's capsule
Afferent and efferent glomerular arterioles
Proximal convoluted tubule
Proximal straight tubule
Thin limb
Thick ascending limb (distal straight tubule)
Distal convoluted tubule
Macula densa
Henle's loop
Collecting ducts

Each kidney possesses an average of 600,000 to 1,400,000 tubular structures called nephrons, which contain a series of histologically distinct segments that alter the concentration and contents of urine. The major segments of each nephron are known as the glomerulus, proximal tubule, thin limb, distal tubule, and collecting duct. The proximal and distal tubules are both divided into convoluted and straight parts, while the thin limb is divided into descending and ascending parts.

The arrangement of these different nephron segments gives rise to the two grossly visible zones in the kidney, known as the cortex and medulla. The medulla is divided into an outer zone (which is further subdivided into outer and inner stripes) and an inner zone. The boundaries of these various regions are marked by the transition sites between different nephron segments, as described later.

GLOMERULUS AND PROXIMAL CONVOLUTED TUBULE

The initial formation of urine occurs at the interface between the glomerular capillaries, which are arranged in a spherical tuft, and the first part of the nephron, an epithelial-lined sac known as Bowman's capsule. The glomerular capillaries and Bowman's capsule are together knows as the glomerulus (or renal corpuscle). As blood from an afferent arteriole passes through the glomerular capillaries, plasma and non–protein bound solutes are filtered into the area bounded by Bowman's capsule, known as Bowman's space, to form primitive urine. All nonfiltered blood is carried away from the glomerular capillaries in an efferent arteriole.

Bowman's space conveys the primitive urine to the first part of the proximal tubule, known as the proximal convoluted tubule, which takes a very tortuous course through a small region of the cortex. The proximal convoluted tubule then transitions to the proximal straight tubule, which is the first part of the loop of Henle.

LOOP OF HENLE

After the proximal convoluted tubule, each nephron plunges into the medulla, makes a hairpin turn, and then returns to the cortex near its parent glomerulus. This region of each nephron is known as the loop of Henle, and it contains the proximal straight tubule, thin limb, and distal straight tubule (more commonly known as the thick ascending limb).

The proximal straight tubule, described above, originates in the cortex and courses to the border between the outer and inner stripes of the outer zone of the medulla. It then transitions to the first part of the thin limb, known as the descending thin limb.

The remaining structure of the loop of Henle differs based on the location of the nephron's parent glomerulus. In nephrons associated with glomeruli in more superficial regions of the renal cortex, the descending thin limb continues until reaching the border between the inner zone of the medulla and the inner stripe of the outer zone of the medulla. At this point, it transitions to the thick ascending limb, which makes a hairpin turn and courses back toward the cortex.

In nephrons associated with glomeruli near the corticomedullary border (known as juxtamedullary glomeruli), the descending thin limb plunges deep into the medulla, makes a hairpin turn near the papilla, and continues as the ascending thin limb until the border between the outer and inner zones of the medulla. At this point it transitions to the thick ascending limb, which courses back toward the cortex.

Thus, based on the above descriptions, two different populations of nephrons can be distinguished: short-looped nephrons, which are associated with superficial and midcortical glomeruli, and long-looped nephrons, which are associated with juxtamedullary glomeruli. Long-looped nephrons have higher urine-concentrating capabilities than short-looped nephrons (see Plate 3-15); however, short-looped nephrons are far more numerous, accounting for 85% of the total nephron population in humans.

DISTAL CONVOLUTED TUBULE, CONNECTING TUBULE, AND COLLECTING DUCT

The thick ascending limb, as described in the previous section, courses from the medulla toward the cortex, where it transitions to the distal convoluted tubule. Near this transition point is a specialized group of cells known as the macula densa, which make direct contact with the nephron's parent glomerulus.

The distal convoluted tubule, like the proximal convoluted tubule, takes a very tortuous course within a small area of the cortex. It transitions to a short connecting segment (or tubule), which in turn leads to the collecting duct.

The collecting duct courses from the cortex toward the medulla adjacent to ducts from neighboring nephrons. In the inner zone of the medulla, these individual ducts join to form larger ducts. By a succession of several such junctions, the papillary ducts are formed, which arrive at the cribriform area of the papillae to drain urine into the minor calyces.

RENAL MICROVASCULATURE

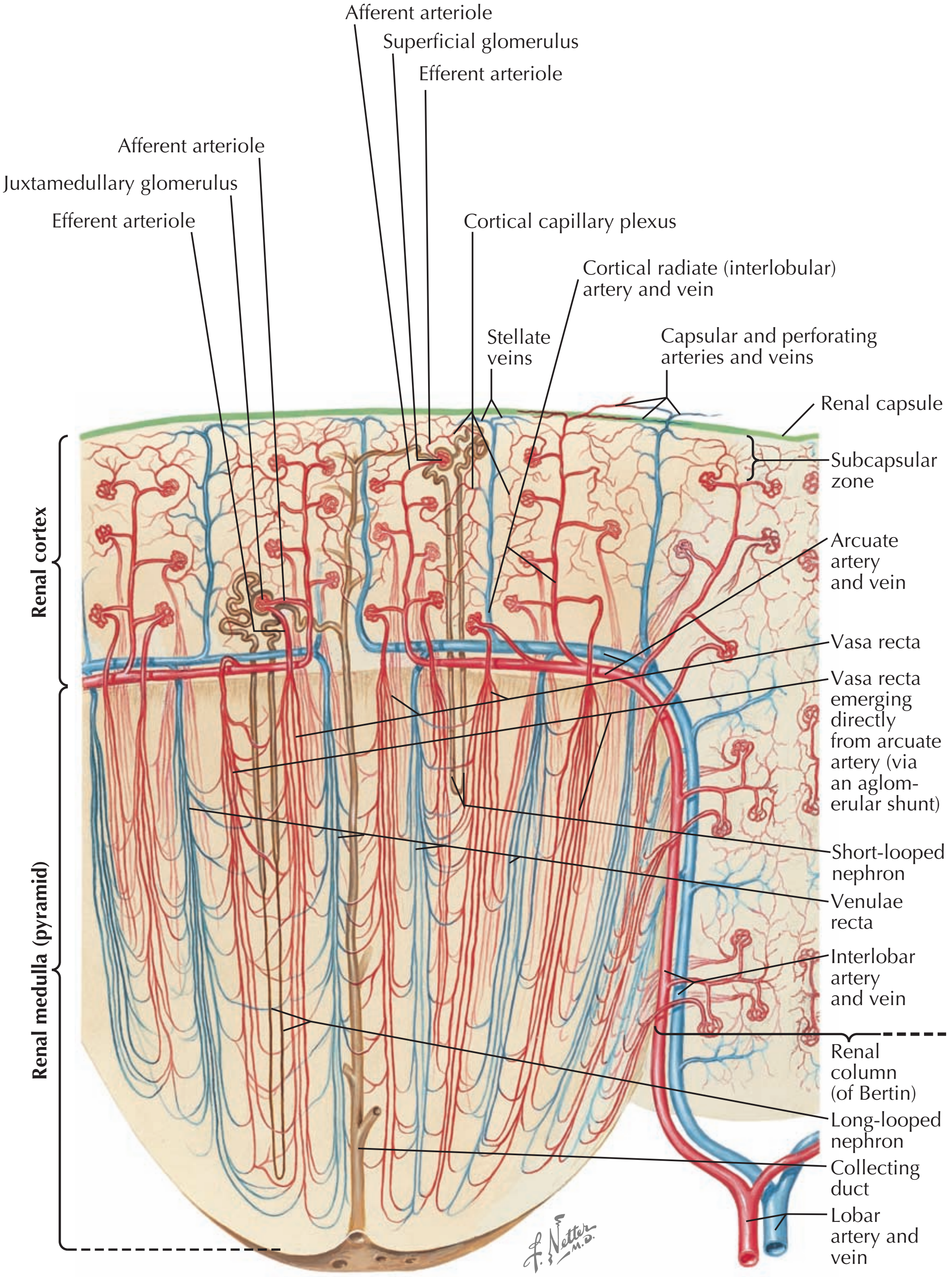
The renal segmental arteries divide into lobar and then interlobar arteries, which enter the renal (cortical) columns and course alongside the pyramids (see Plate 1-10). As each interlobar artery approaches the base of its adjacent pyramid, it divides into several arcuate arteries.

Both interlobar and arcuate arteries give rise to cortical radiate (interlobular) arteries. Those cortical radiate (interlobular) arteries that reach the fibrous capsule form capsular and perforating branches that communicate with extracapsular vessels. The capsular and perforating veins, as well as a dense subcapsular plexus of stellate veins, drain into the cortical radiate (interlobular) veins, which drain into the arcuate and then interlobar veins.

The main purpose of the cortical radiate (interlobular) arteries, however, is to give rise to afferent arterioles. Each afferent arteriole gives rise to a glomerulus, which is responsible for filtering blood into a nephron. Afferent arterioles located near the outer cortex give rise to superficial and midcortical glomeruli, associated with short-looped nephrons, while afferent arterioles located in the inner cortex give rise to juxtamedullary glomeruli, associated with long-looped nephrons.

In both cortical and juxtamedullary glomeruli, the blood that remains in the glomerular capillaries after filtration drains into efferent arterioles. Because the glomerular capillary bed thus lies between two arterioles, an arrangement not seen elsewhere in the vasculature, the pressure across the capillary walls can be very finely adjusted in response to homeostatic demands.

The appearance and branching pattern of the efferent arterioles differ based on the glomerulus type.


Afferent arteriole
Superficial glomerulus
Efferent arteriole
Afferent arteriole
Juxtamedullary glomerulus
Efferent arteriole
Cortical capillary plexus
Cortical radiate (interlobular) artery and vein
Stellate veins
Capsular and perforating arteries and veins
Renal capsule
Subcapsular zone
Arcuate artery and vein
Vasa recta
Vasa recta emerging directly from arcuate artery (via an aglomerular shunt)
Short-looped nephron
Venulae recta
Interlobar artery and vein
Renal column (of Bertin)
Long-looped nephron
Collecting duct
Lobar artery and vein
Renal cortex
Renal medulla (pyramid)
F. Netter M.D.

SUPERFICIAL GLOMERULI

At superficial glomeruli, the efferent arterioles are small, containing only one layer of smooth muscle cells. These arterioles divide into a dense plexus of peritubular capillaries, which surrounds the cortical segments of short-looped nephrons. This plexus drains into the cortical radiate (interlobular), arcuate, and then interlobar veins.

The peritubular capillaries have fenestrae that contain negatively charged diaphragms, which permit a selective exchange of materials with adjacent tubules. These diaphragms consist of 7-nm wide, criss-crossed fibrils that intersect at a central area like spokes of a wheel. In addition, tiny microfibrils anchor the peritubular capillaries to the basement membranes of the renal tubules, holding these structures in close approximation.

JUXTAMEDULLARY GLOMERULI

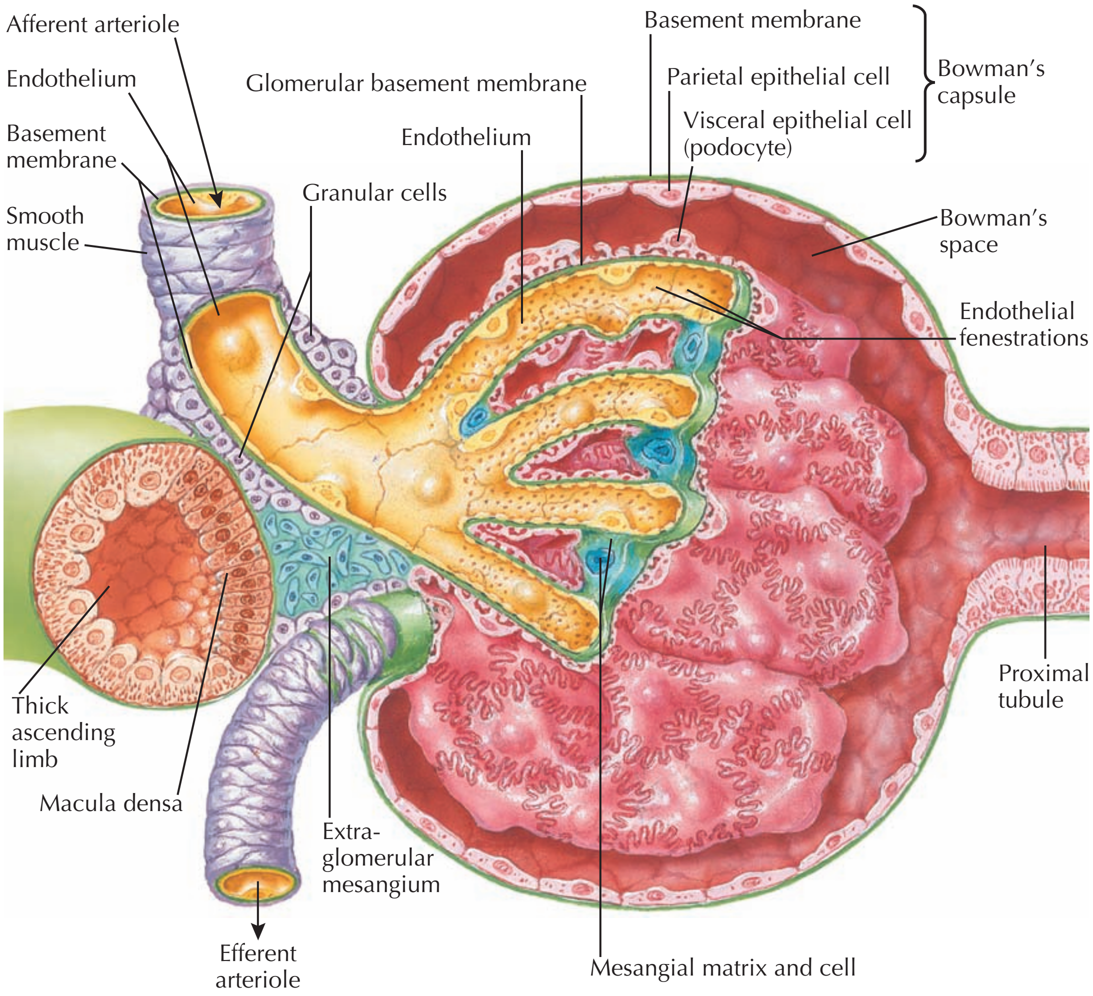
At juxtamedullary glomeruli, the efferent arterioles are larger and contain multiple layers of smooth muscle cells. Some of these arterioles form a capillary plexus that surrounds the cortical segments of long-looped nephrons. Most, however, descend directly into the medulla as long branching loops known as vasa recta, which travel parallel to the loops of Henle and collecting ducts. The vessels of the (descending) vasa recta make hairpin turns in the inner medulla to become (ascending) venulae recta, which return to the corticomedullary junction and drain into arcuate and then interlobar veins.

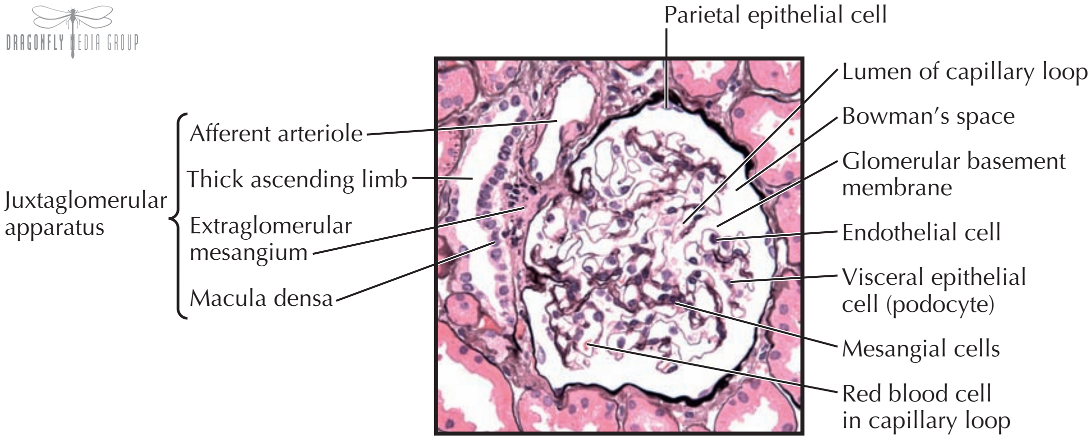
The vessels of the (descending) vasa recta contain a layer of smooth muscle cells that regulate flow in response to hormonal input. The endothelial cells that line the inner surface of the vessels are continuous and nonfenestrated. The vessels of the (ascending) venulae recta, in contrast, do not contain a smooth muscle layer, and their endothelial cells are fenestrated. The functional significance of these differences is not well understood.

The association of vasa recta with the loops of Henle and collecting ducts forms the anatomic substrate for the countercurrent exchange system, which is critical for the production of concentrated urine (see Plate 3-12). Some illustrations depict each individual nephron as being consistently associated with the vasa recta derived from its own efferent arteriole. It is now understood, however, that each nephron is invested with vasa recta derived from numerous efferent arterioles.

Advanced age and certain types of chronic kidney disease are associated with degeneration of glomerular vessels. In the cortex, this is often enough to obliterate postglomerular flow altogether. Near the medulla, where the efferent arterioles are thicker, such degeneration gives rise to aglomerular shunts that connect afferent and efferent arterioles. In this case, vasa recta may emerge directly from arcuate and interlobular arteries.

STRUCTURE AND HISTOLOGY OF THE GLOMERULUS


Afferent arteriole
Endothelium
Basement membrane
Smooth muscle
Glomerular basement membrane
Endothelium
Granular cells
Basement membrane
Parietal epithelial cell
Visceral epithelial cell (podocyte)
Bowman's capsule
Bowman's space
Endothelial fenestrations
Proximal tubule
Thick ascending limb
Macula densa
Extra-glomerular mesangium
Efferent arteriole
Mesangial matrix and cell


Parietal epithelial cell
Lumen of capillary loop
Bowman's space
Glomerular basement membrane
Endothelial cell
Visceral epithelial cell (podocyte)
Mesangial cells
Red blood cell in capillary loop
Juxtaglomerular apparatus
Afferent arteriole
Thick ascending limb
Extraglomerular mesangium
Macula densa

Light microscopy of a normal glomerulus (silver stain, 40× magnification).

GLOMERULUS

The glomerulus (or renal corpuscle) consists of the glomerular capillaries and the epithelium-lined sac that surrounds and invests them, known as Bowman's capsule.

The glomerular capillaries originate from the afferent arteriole and drain into an efferent arteriole. They are arranged in a tuft about 200 μm in diameter, which is anchored to a central stalk of mesangial cells and matrix. The walls of the glomerular capillaries contain three layers. The innermost layer consists of endothelial cells. The second layer consists of glomerular basement membrane (GBM). The outermost layer consists of podocytes, also known as visceral epithelial cells.

Bowman's capsule, the first part of the nephron, consists of the two layers of epithelial cells that invest the glomerular capillaries. The podocytes (visceral epithelial cells) in the capillary wall constitute the inner layer of Bowman's capsule. The parietal epithelial cells, which are continuous with the podocytes at the base of the capillary tuft, constitute its outer layer. The area between the podocyte and parietal epithelial cell layers is known as Bowman's space.

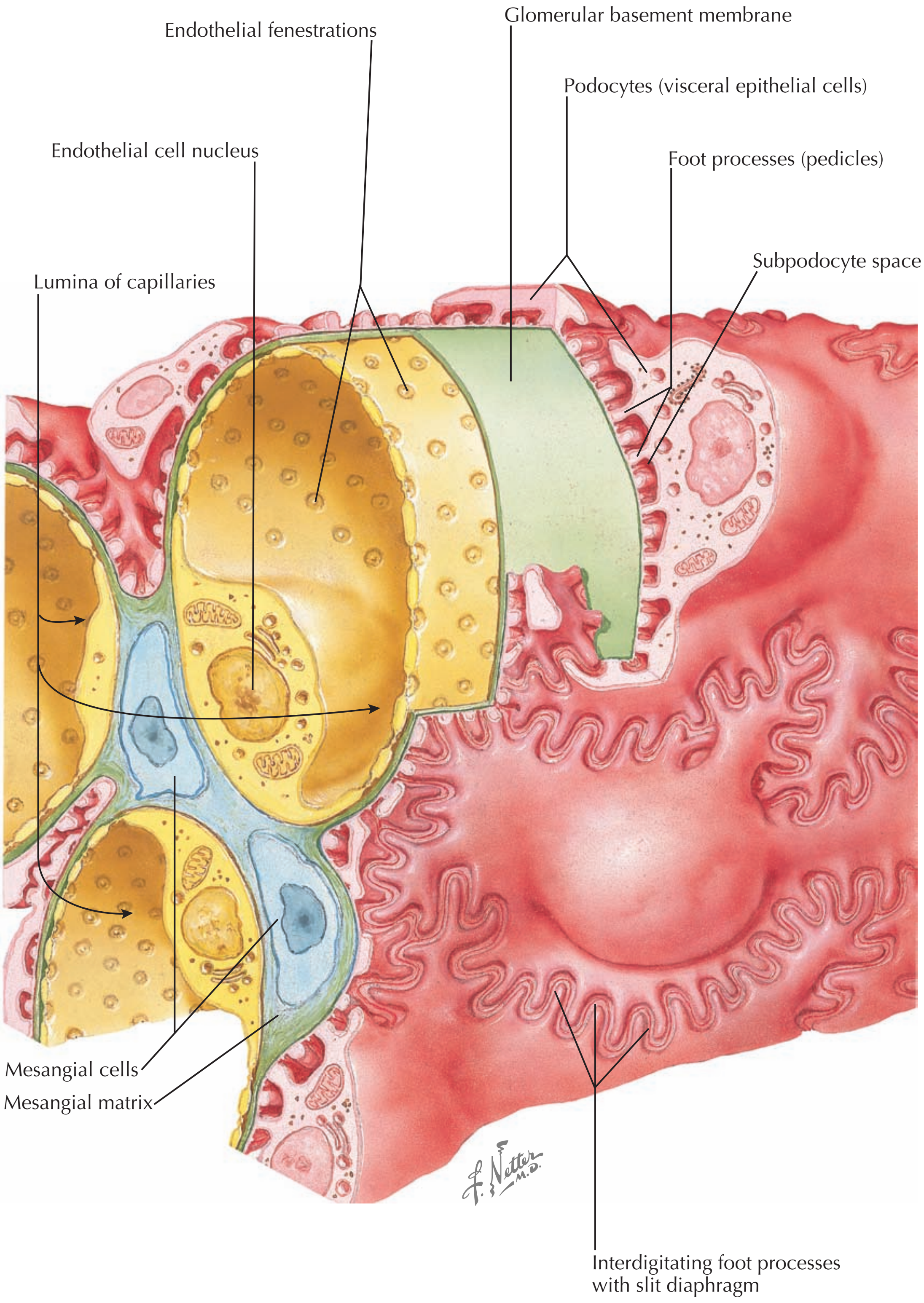
THE CAPILLARY WALL

As blood passes through the glomerular capillaries, plasma and small, non–protein bound solutes are freely filtered across the three layers of the capillary wall into Bowman's space, which leads to the proximal tubule. These three capillary wall layers, however, act as a critical barrier to the filtration of cells and larger plasma molecules, such as proteins, based on their size and charge.

The endothelial cells, which line the inner surface of the capillaries, are inconspicuous and possess a thin, attenuated cytoplasm. Their nuclei are generally located near the mesangial stalk, so as not to interfere with filtration. These cells contain fenestrations that are approximately 70 to 100 nm in diameter, which may serve as an initial size-based filtration barrier. The cell surfaces are also coated with a negatively charged glycocalyx that projects into the fenestrations and provides a charge-based filtration barrier.

The GBM lines the outer surface of the endothelial cells and is continuous with the basement membrane of Bowman's capsule. It is synthesized by both endothelial cells and podocytes, and it consists of three layers: a thin lamina rara interna, a thick central lamina densa, and a thin lamina rara externa. Together, these layers measure approximately 300 to 350 nm across, being somewhat thicker in males than in females. The GBM consists primarily of type IV collagen and other proteins, such as laminin and nidogen (also known as entactin). The tight arrangement of these proteins contributes to the size-based filtration barrier. In addition, the GBM contains negatively charged proteoglycans

FINE STRUCTURE OF THE GLOMERULUS


Endothelial fenestrations
Glomerular basement membrane
Podocytes (visceral epithelial cells)
Endothelial cell nucleus
Foot processes (pedicles)
Subpodocyte space
Lumina of capillaries
Mesangial cells
Mesangial matrix
Interdigitating foot processes with slit diaphragm
F. Netter M.D.

GLOMERULUS *(Continued)*

that contribute to the charge-based filtration barrier. The potential space between the endothelial cells and GBM is known as the subendothelial space, while the potential space between the GBM and the podocytes is known as the subepithelial space.

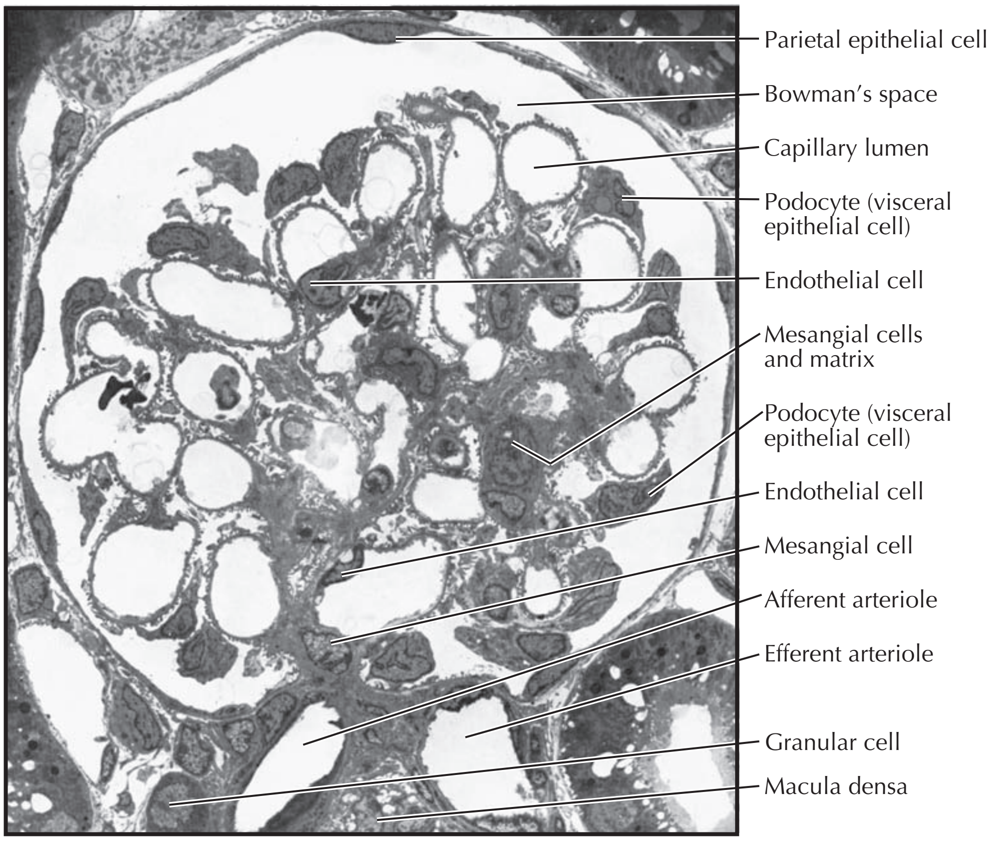
The podocytes are large cells with prominent nuclei and other intracellular organelles. Their cytoplasm is elaborately drawn out into long processes that give rise to fingerlike projections known as foot processes (pedicels). These foot processes attach to the outer surface of the GBM and interdigitate with those from adjacent podocytes. They also lie between the podocyte cell bodies and the GBM, forming a subpodocyte space. The space between adjacent foot processes is generally about 25 to 60 nm. A structure known as the slit diaphragm spans this distance. It consists of an 11 nm-wide central filament attached to adjacent podocyte cell membranes by cross-bridging proteins arranged in a zipper-like configuration. The pores formed between the central filament, cell membranes, and cross-bridges have been measured as approximately 4 × 14 nm. These small pores in the slit diaphragm make a critical contribution to the size-based filtration barrier. In addition, the podocytes are lined by a negatively-charged glycocalyx, which likely contributes to the charge-based barrier.

The relative contributions of the three layers of the capillary wall to the filtration barrier remain controversial. The slit diaphragm is likely the main obstacle to protein diffusion. Indeed, glomerular diseases that cause loss of protein into the urine (proteinuria) generally cause a process known as foot process effacement, in which foot processes retract and shorten, disrupting slit diaphragms and opening a wide space for the passage of proteins. Nonetheless, disruption of the endothelial layer or GBM has also been shown to cause proteinuria, suggesting that these layers also make important contributions.

ADDITIONAL CELL TYPES

The mesangial cells provide structural support to the glomerular capillaries. These cells are irregularly shaped and send long cytoplasmic processes between endothelial cells. They are similar to modified smooth muscle cells and stain positive for smooth muscle actin and myosin. These cells can contract in response to various signals, narrowing the capillary loops and reducing glomerular flow. Signals that modulate mesangial tone include angiotensin II (see Plate 3-18), antidiuretic hormone (see Plate 3-17), norepinephrine, and thromboxane. In addition, mesangial cells are capable of phagocytosing local macromolecules and immune complexes, as well as generating inflammatory

ELECTRON MICROSCOPY OF THE GLOMERULUS

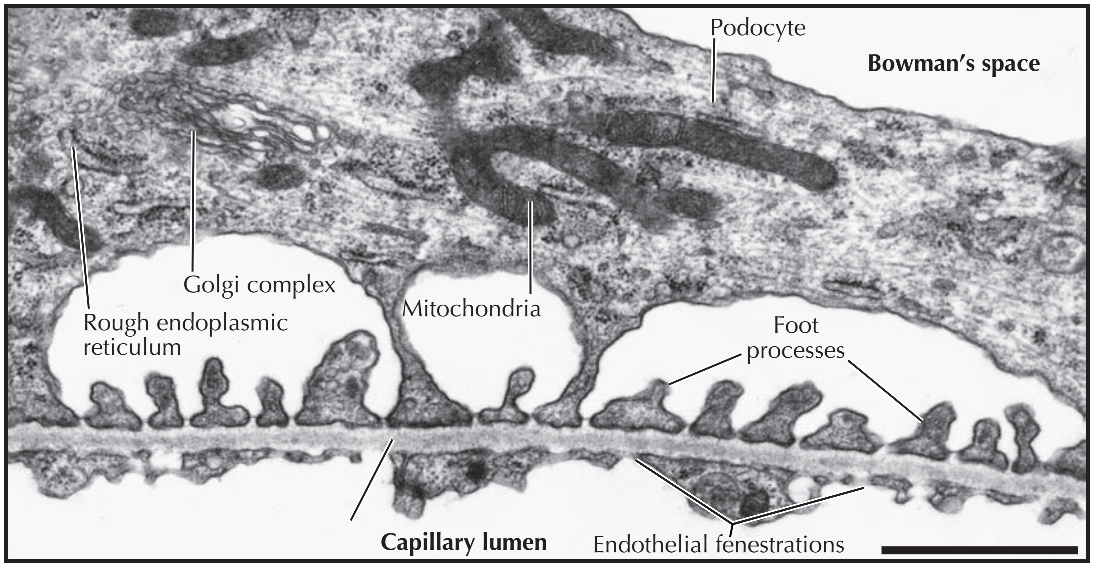

Parietal epithelial cell
Bowman's space
Capillary lumen
Podocyte (visceral epithelial cell)
Endothelial cell
Mesangial cells and matrix
Podocyte (visceral epithelial cell)
Endothelial cell
Mesangial cell
Afferent arteriole
Efferent arteriole
Granular cell
Macula densa

× 1100

GLOMERULUS *(Continued)*

mediators in response. The mesangial cells are embedded in the mesangial matrix, which contains collagen, various proteoglycans, and other molecules. In histologic sections of normal glomeruli, one or two mesangial cells are typically seen per matrix area, with a greater number seen in certain pathologic states.

The parietal epithelial cells are flat squamous cells with sparse organelles. They are continuous with the visceral epithelial cells near the base of the glomerular capillary tuft and with the cells of the proximal tubule at the opposite side of the glomerulus. In histologic sections of normal glomeruli, one or two layers of parietal epithelial cells may be seen. In severe, rapidly progressive glomerular disease, additional layers of parietal cells may be seen.


Podocyte
Bowman's space
Golgi complex
Mitochondria
Rough endoplasmic reticulum
Foot processes
Capillary lumen
Endothelial fenestrations

Fine details of capillary wall. *Reprinted with permission from Ovalle W, Nahirney P. Netter's Essential Histology. Philadelphia, Saunders, 2008.*

THE JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus is a specialized structure that consists of components from both the glomerulus and the distal tubule of its associated nephron.

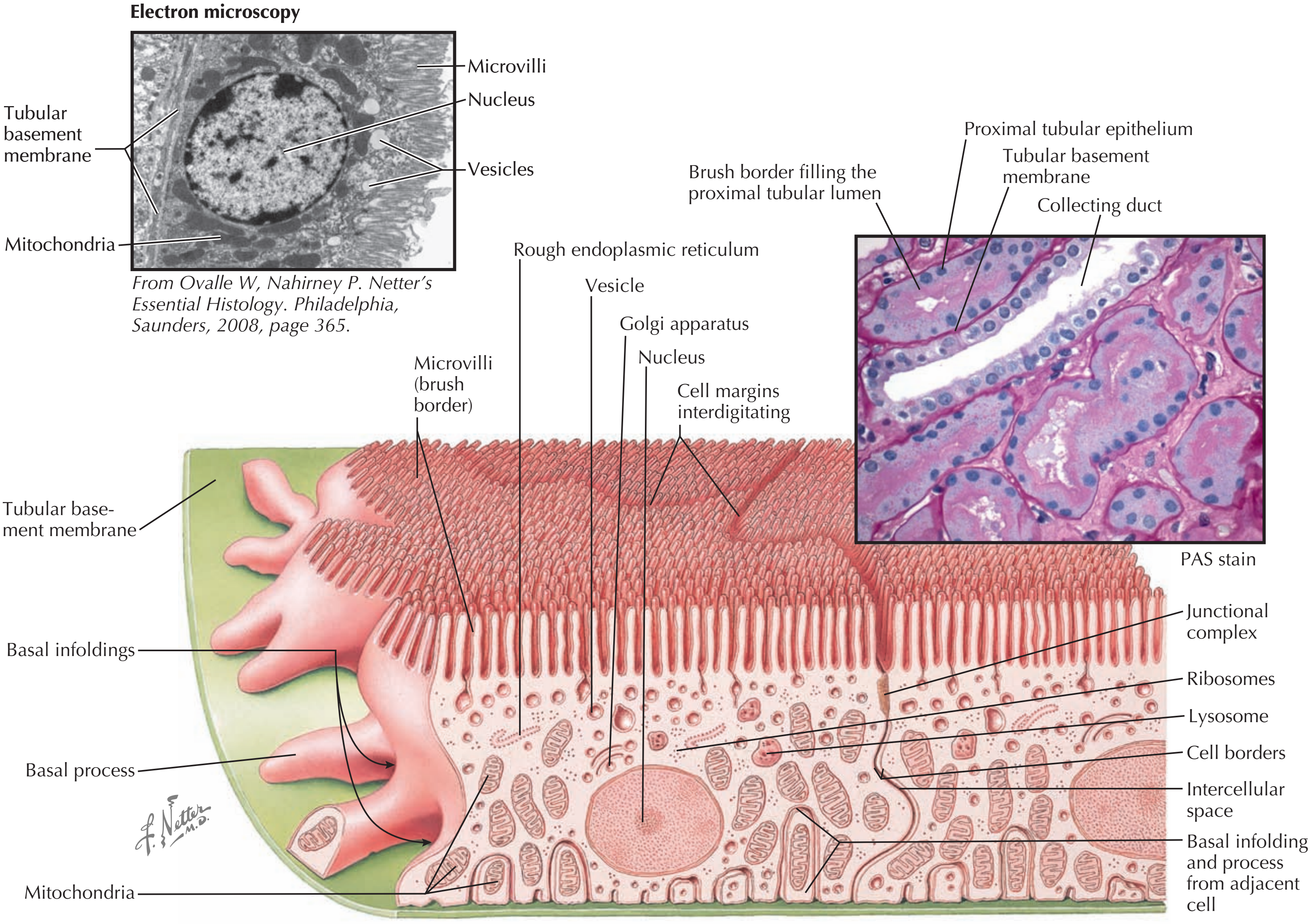
The glomerular components include the terminal afferent arteriole, initial efferent arteriole, and extraglomerular mesangium (also known as the lacis or as the cells of Goormaghtigh). The nephron supplied by this glomerulus loops around so that its thick ascending limb contacts the extraglomerular mesangium. The region of the thick ascending limb that makes direct contact with the extraglomerular mesangium contains specialized cells and is known as the macula densa.

Because of this arrangement, the distal tubule is able to provide feedback to the glomerulus to modulate the filtration rate. In the setting of inadequate tubular flow, for example, the macula densa triggers dilation of the afferent arteriole, which increases the filtration rate, and stimulates renin secretion from specialized cells, known as granular cells, in the walls of the afferent and efferent arterioles. (For details, see Plate 3-18.)

The extraglomerular mesangial cells are continuous with and resemble normal mesangial cells. They are linked to the granular cells via gap junctions, and they share a basement membrane and interstitium with the adjacent macula densa cells. Thus the extraglomerular mesangium appears to serve as the signaling intermediary between the tubular and vascular components of the juxtaglomerular apparatus.

The granular cells are similar to ordinary smooth muscle cells but have sparser smooth muscle myosin and contain numerous renin-filled vesicles. Because they produce large quantities of hormones, these cells also feature a prominent endoplasmic reticulum and Golgi apparatus.

Finally, the macula densa cells appear distinct from the neighboring tubular cells; a detailed description is available on Plate 1-25.



Electron microscopy

Microvilli
Nucleus
Tubular basement membrane
Vesicles
Mitochondria

From Ovalle W, Nahirney P. Netter's Essential Histology. Philadelphia, Saunders, 2008, page 365.

Proximal tubular epithelium
Tubular basement membrane
Brush border filling the proximal tubular lumen
Collecting duct

PAS stain

Rough endoplasmic reticulum
Vesicle
Golgi apparatus
Nucleus
Microvilli (brush border)
Cell margins interdigitating
Tubular basement membrane
Basal infoldings
Basal process
Mitochondria
Junctional complex
Ribosomes
Lysosome
Cell borders
Intercellular space
Basal infolding and process from adjacent cell
F. Netter M.D.

Stereogram of proximal convoluted tubular epithelium

PROXIMAL TUBULE

The proximal tubule receives urine from Bowman's space. It plays a major role in the transport of material from the urine back into the blood (reabsorption) and vice versa (secretion). In humans, the entire proximal tubule is approximately 14 mm long. It is divided into two sections: the proximal convoluted tubule (pars convoluta) and the proximal straight tubule (pars recta). The latter forms the first part of the loop of Henle.

In rats, the proximal tubule is often subdivided into S1 (first two thirds of the convoluted part), S2 (last third of the convoluted part and initial portion of the straight part), and S3 (remainder of the straight part); however, these distinctions are generally not made in humans.

The proximal tubule contains cuboidal to low columnar cells arranged over a tubular basement membrane. These cells possess an eosinophilic cytoplasm, and their round nuclei are usually situated near the cell base. Their other histologic features differ according to the particular region under consideration.

PROXIMAL CONVOLUTED TUBULE

The proximal convoluted tubule (PCT) is the major site of solute reabsorption in the nephron. An extensive microvillous brush border on the apical plasma membrane projects into the lumen and dramatically increases the available surface area for solute transport. On light microscopy, the lumen often appears collapsed or indistinct owing to the presence of the brush border, which should be readily seen. Distal tubules and collecting ducts, in contrast, lack a brush border and thus appear more widely patent.

The lateral and basal borders of PCT cells are thrown into extensive processes that interdigitate with infoldings of adjoining cells; as a result, lateral cell borders are indistinct on light microscopy sections. These basolateral processes increase the surface area available for transport across the basolateral cell membrane. They are replete with additional mitochondria to support active transport processes. The complex extracellular area between these folds is known as the basolateral intercellular space. It is closed by the tubular basement membrane, which separates the tubular epithelium from the interstitium and peritubular capillaries.

Junctional complexes connect neighboring cells near their apical surface. These consist of a tight junction (zonula occludens) and an intermediate junction (zonula adherens). Although tight junctions are critical for maintaining the barrier between the tubular lumen and interstitium, a small number of discontinuities permits some molecules to be reabsorbed through a paracellular route.

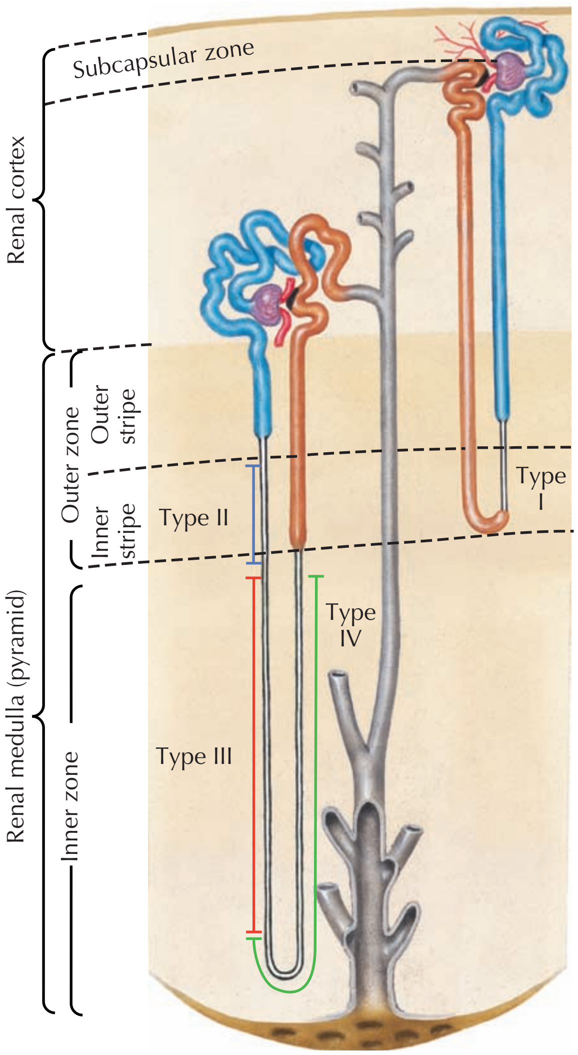
PCT cells are rich with mitochondria, which provide energy for solute transport. These are arranged perpendicular to the cell base and resemble vertical striations on some histologic sections. These cells also possess a prominent rough endoplasmic reticulum and Golgi apparatus near the apical membrane.

PCT cells contain evidence of extensive endocytosis near the apical plasma membrane, including coated pits, invaginations, and endosomes. Numerous lysosomes are also present to process and degrade a subset of the incoming material. Endocytosis appears to be most important for the reabsorption of filtered proteins, as it is up-regulated in conditions that damage the normal glomerular filtration barrier.

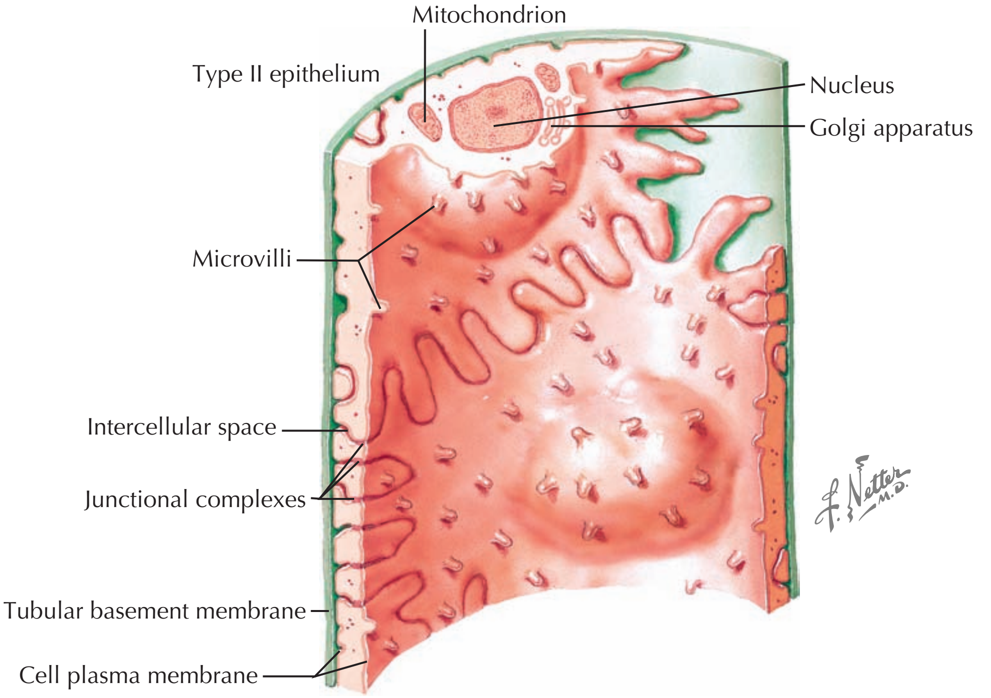
PROXIMAL STRAIGHT TUBULE

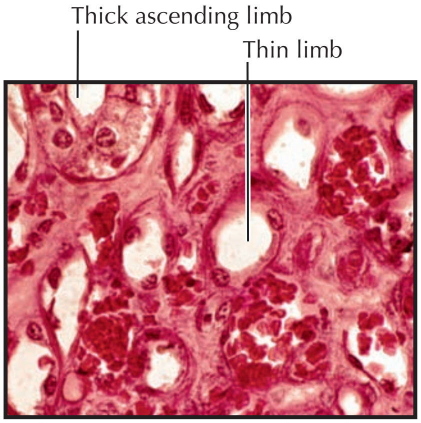
The cells of the proximal straight tubule differ from those of the PCT in several important respects. The microvilli are shorter and sparser, endocytotic figures are less frequent, mitochondria are sparser, and the basolateral processes and infoldings are smaller and less elaborate. These morphologic differences reflect the smaller amount of reabsorption that occurs across these cells.

Distribution of thin limb cell types in several mammals

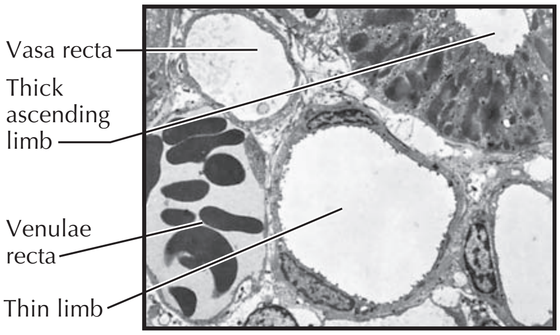

Subcapsular zone
Renal cortex
Outer zone
Outer stripe
Inner stripe
Type II
Type I
Type IV
Type III
Renal medulla (pyramid)
Inner zone

Stereogram of thin limb epithelium


Mitochondrion
Type II epithelium
Nucleus
Golgi apparatus
Microvilli
Intercellular space
Junctional complexes
Tubular basement membrane
Cell plasma membrane
F. Netter M.D.


Thick ascending limb
Thin limb

Light microscopy: section through renal medulla (H&E stain, ×680)


Vasa recta
Thick ascending limb
Venulae recta
Thin limb

Electron microscopy: section through renal medulla (×4000)

Thin Limb

The thin limb receives urine from the proximal straight tubule and also contributes to the loop of Henle. It contains descending and ascending parts, which are both key components of the countercurrent multiplication system that promotes concentration of urine (details on Plate 3-12).

The transition from the proximal straight tubule to the thin limb involves a sharp change from cuboidal and low columnar cells to simple, largely flat epithelium. It occurs at the border of the outer and inner stripes of the outer medulla.

The length of the thin segment differs depending on nephron type. In short-looped nephrons, the descending thin limb reaches the border of the outer and inner zones of the medulla and then transitions to the thick ascending limb. Meanwhile, in long-looped nephrons, the descending thin limb continues deep into the inner zone of the medulla, makes a hairpin turn, becomes the ascending thin limb, and then transitions to the thick ascending limb at the border between the outer and inner zones of the medulla. Thus, although both nephron types feature a descending thin limb, only juxtamedullary nephrons feature an ascending thin limb.

Four morphologically distinct types of cells have been described in thin limbs of several mammals, and each cell type appears to have its own physiologic significance (discussed on Plate 3-15). It is unclear if these same cell types exist in humans.

TYPE I CELLS

Type I cells are found throughout the descending thin limbs of short-looped nephrons. They are short, with few microvilli or basolateral interdigitations, as well as scant mitochondria or other organelles. Their nuclei bulge into the tubular lumen. Neighboring cells are joined by multistranded tight junctions and desmosomes, which restrict paracellular transport.

TYPE II-IV CELLS

Type II-IV cells are found in the thin limbs of long-looped nephrons.

Type II cells are seen in the descending thin limb in the outer zone of the medulla. They are taller than type I cells, with more numerous microvilli and basolateral interdigitations. In addition, the tight junctions are single-stranded and thus somewhat leaky, permitting paracellular transport. Of the four cell types, type II cells show the most interspecies variation.

Type III cells are seen in the descending thin limb in the inner zone of the medulla. These cells are shorter than type II cells, with fewer microvilli and interdigitations. Their tight junctions are well-developed, restricting paracellular transport.

Type IV cells are seen just before the hairpin turn of the descending thin limb and are present for the remainder of the ascending thin limb. These cells are completely flattened and have no microvilli, like type I epithelium, but they have an increased number of basolateral interdigitations. Their tight junctions are leaky, permitting paracellular transport.

DISTAL TUBULE

The distal tubule receives urine from the thin limb. Like the proximal tubule, the distal tubule is divided into two major sections. The first is known as the thick ascending limb (also known as the distal straight tubule, or pars recta), and the second is known as the distal convoluted tubule (pars convoluta). Just before the transition to the distal convoluted tubule, the thick ascending limb touches its parent glomerulus, and the epithelial cells that make direct contact constitute a specialized structure known as the macula densa.

In short-looped nephrons, the thick ascending limb accounts for the entire ascending limb of the loop of Henle. In contrast, in long-looped nephrons, the thin limb accounts for the initial part of the ascending limb, then transitions to the thick ascending limb at the border of the inner and outer zones of the medulla.

THICK ASCENDING LIMB

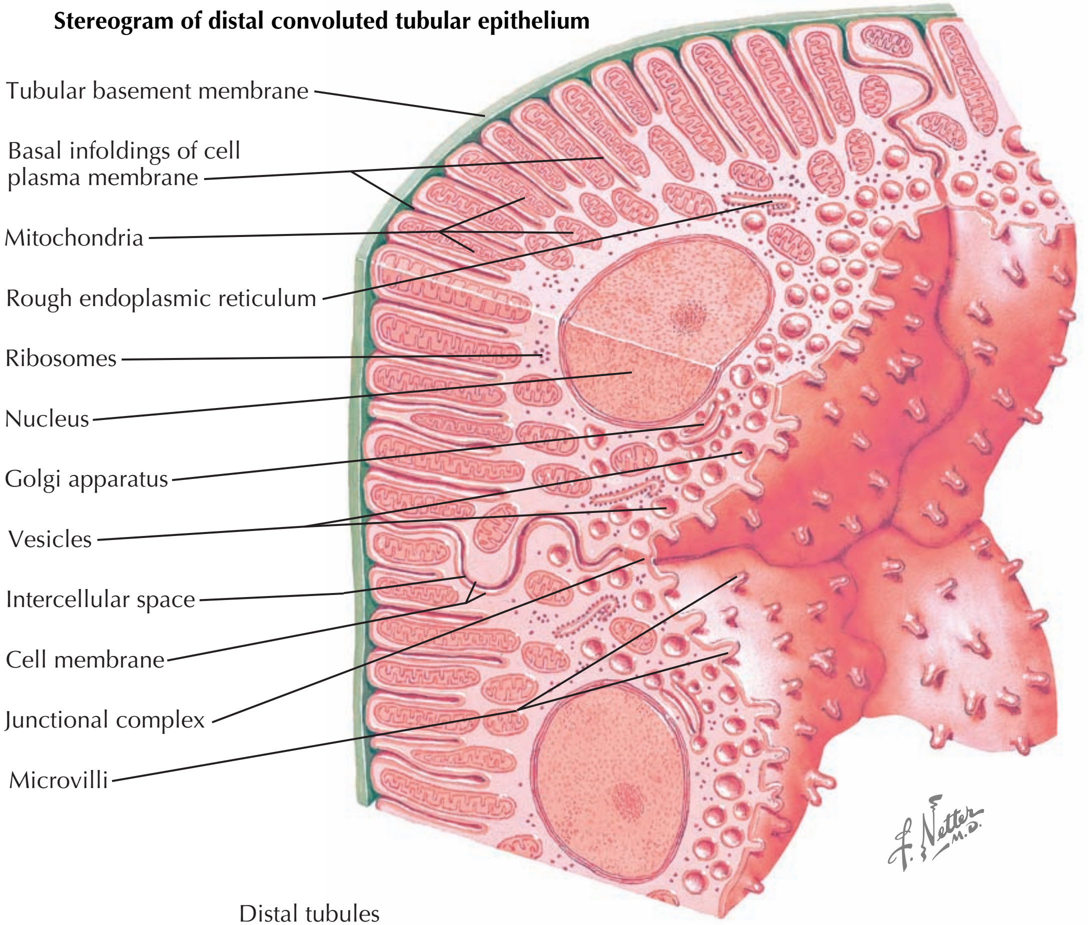
The thick ascending limb (TAL) plays an important role in the reabsorption of ions and is crucial for maintenance of the countercurrent multiplication system, described on Plate 3-12.

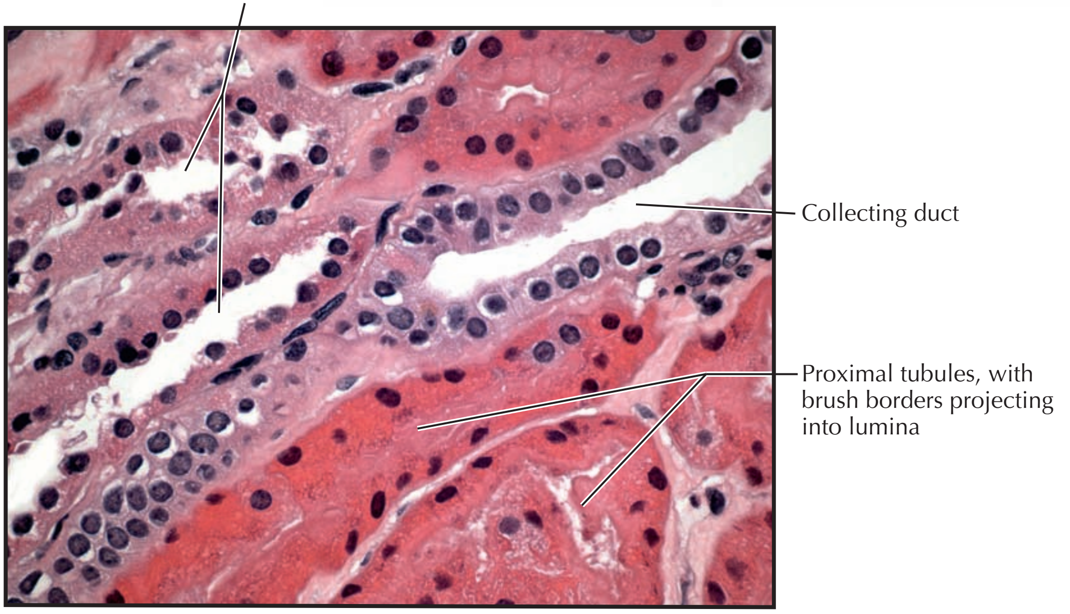
The cells of the TAL are low cuboidal. Their height decreases as the tubule progresses from medulla to cortex. Their apical surfaces are dotted with sparse, short microvilli. In the rat, there is a subset of "rough" cells, which have sparse microvilli, and "smooth cells," which lack them altogether. The relative proportion of "rough" cells increases as the tubules approach the renal cortex. Because of the scarcity of microvilli, the distal tubules appear patent on light microscopy, facilitating the distinction from proximal tubules, which possess a well-developed brush border.

Below the apical surface are numerous small vesicles, which traffic ion channels and transporters to the plasma membrane. The rough endoplasmic reticulum and Golgi apparatus, which synthesize these proteins, are prominent. The nuclei are located near the apical membrane and sometimes bulge out toward the lumen.

The basolateral membranes are thrown into extensive, interdigitating processes and infoldings, which increase the surface area available for basolateral transport. As a result of this configuration, the lateral cell borders appear indistinct on light microscopy sections. The basolateral processes are filled with mitochondria, which resemble striations on histologic sections, to provide energy for active transport. Interdigitating processes and infoldings from neighboring cells are joined together by tight junctions.

Stereogram of distal convoluted tubular epithelium





H&E stain

MACULA DENSA

Unlike the rest of the distal tubular cells, the macula densa cells are columnar and lack extensive interdigitating basolateral processes. Their high nucleus to cytoplasmic ratio causes them to appear denser than neighboring cells. Their nuclei are positioned near their apical surface, above most of the cellular organelles. The basal surfaces of these cells interdigate with the adjacent extraglomerular mesangium through their shared basement membrane, reflecting their physiologic connection.

DISTAL CONVOLUTED TUBULE

At some distance after the macula densa, there is an abrupt transition from the low cuboidal cells of the TAL to the taller cuboidal cells of the distal convoluted tubule, which takes a tortuous course through a small area of cortex. The cells of the distal convoluted tubule have more numerous apical microvilli than those of the TAL, but their other features are similar.

CONNECTING SEGMENT

At the end of the distal tubule, just before the transition to the collecting duct, there is a zone known as the connecting segment (or tubule). This segment lacks clear boundaries and mixes gradually with the previous and next segments. In general, however, the cells in this segment have less prominent interdigitating membrane processes and fewer mitochondria than those of the DCT. Principal and intercalated cells, which figure prominently in the collecting duct, begin to appear in this segment.

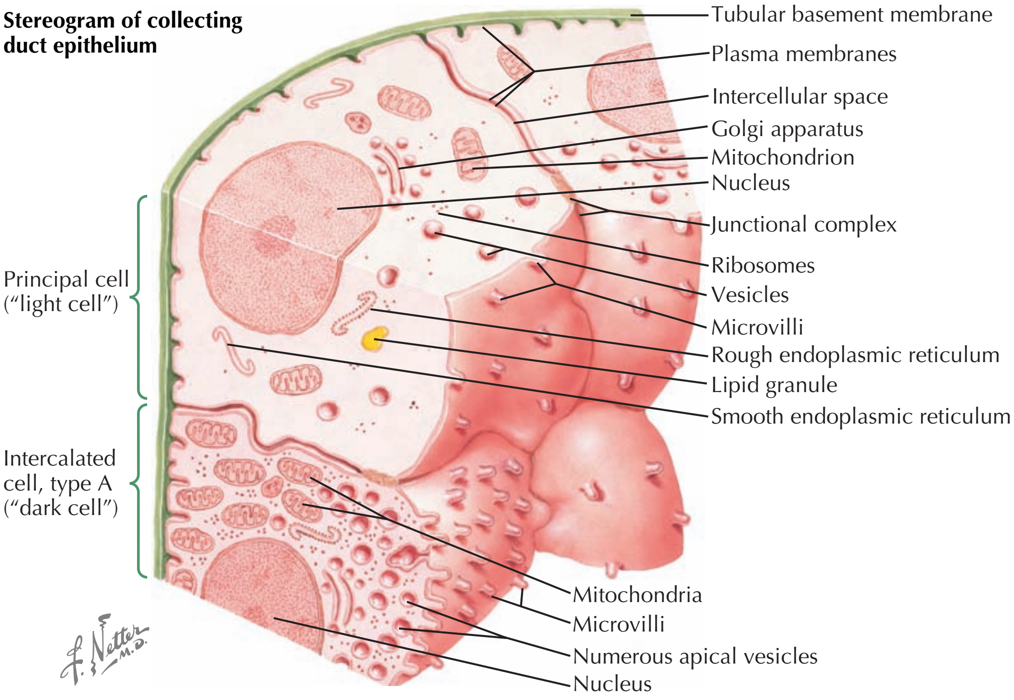
COLLECTING DUCT

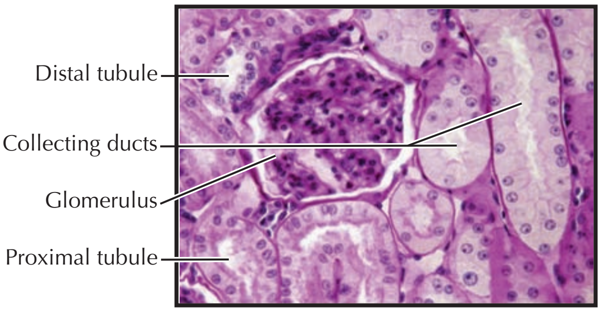
The collecting ducts receive urine from the connecting segments (or tubules). The ducts extend from cortex to medulla, and they are customarily divided into cortical, outer medullary, and inner medullary regions. As the ducts course toward the medulla, they fuse into progressively larger conduits that ultimately terminate at the cribriform area of the renal papillae, where urine drains into the minor calices.

The collecting duct develops from the ureteric bud (see Plate 2-1) and is thus technically not part of the nephron. Nonetheless, these ducts play a key role in determining the final composition of urine and do not serve as mere conduits to the renal papillae.

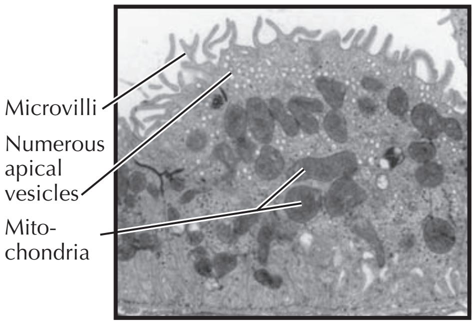
The collecting ducts are easily distinguished on light microscopic sections because their cells have distinct and straight borders, no apical brush border, round and central nuclei, and light to clear cytoplasms. In cross section, the collecting ducts have large, patent lumina, which can be distinguished from the narrow, collapsed lumina of proximal tubules.

Stereogram of collecting duct epithelium

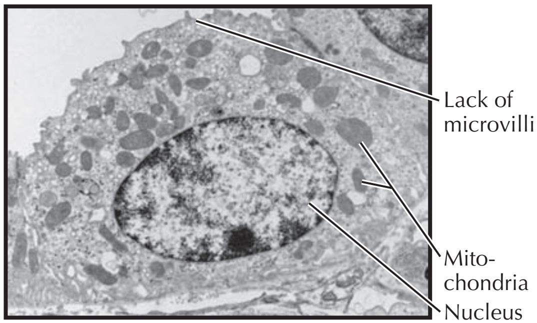




Light microscopy (PAS stain).
From Ovalle W. Nahirney P. Netter's Essential Histology. Philadelphia, Saunders, 2008. page 369



Electron microscopy. Type A intercalated cell in cortical collecting duct of mouse (nucleus not seen in section)



Electron microscopy. Type B intercalated cell in cortical collecting duct of mouse

CORTICAL COLLECTING DUCT

The cortical collecting duct contains two major cell types: principal ("light") cells and intercalated ("dark") cells. Principal cells transport salt and water, while intercalated cells participate in acid-base homeostasis. Although these cell types can be distinguished using electron microscopy, they often appear similar on light microscopy sections.

Principal cells have relatively few intracellular organelles and thus their cytoplasm appears "light" using some staining techniques. These cells are cuboidal in appearance. Their apical membranes have sparse, short microvilli. Their basal surface contains few short invaginations, while the lateral surfaces contain very few small processes and infoldings. Unlike in the proximal and distal tubules, mitochondria are not localized to the basolateral processes and are instead scattered throughout the cytoplasm. Extensive water reabsorption occurs across these cells, as described on Plate 3-15, which causes the appearance of a prominent intercellular space. The cells are connected to one another by tight junctions and desmosomes.

Intercalated cells, in contrast, are dense with mitochondria and other organelles, which cause their cytoplasm to appear "dark" using some staining techniques. These cells are generally subclassified into type A and B intercalated cells (see Plates 3-21 and 3-22).

Type A intercalated cells secrete protons into urine and reabsorb bicarbonate into the interstitium. Their apical surface is dotted with numerous microvilli. The cells also contain numerous vesicles near their apical membrane that contain proton transporters. In acidotic conditions, these vesicles fuse with the apical plasma membrane to increase proton secretion. In chronic acidotic states, these cells become hypertrophic, especially at their apical aspect.

Type B intercalated cells, meanwhile, secrete bicarbonate into urine and pump protons into the interstitium. These cells usually lack the apical features characteristic of type A cells, such as microvilli and a dense vesicle population, which may reflect the reversed polarity of proton pumping. In chronic alkalotic states, these cells become hypertrophic.

The different intercalated cell types may sometimes be distinguished by morphologic characteristics; however, the most reliable means of classifying a particular cell is to examine the population and distribution of its ion transporters using immunostaining. Type A cells express basolateral AE1 HCO$_3^-$/Cl$^-$ exchangers, whereas type B cells express apical pendrin HCO$_3^-$/Cl$^-$ exchangers. Although recent work in some animals points to the existence of a third population of cells, known as non-A non-B cells, their function is not well understood at present.

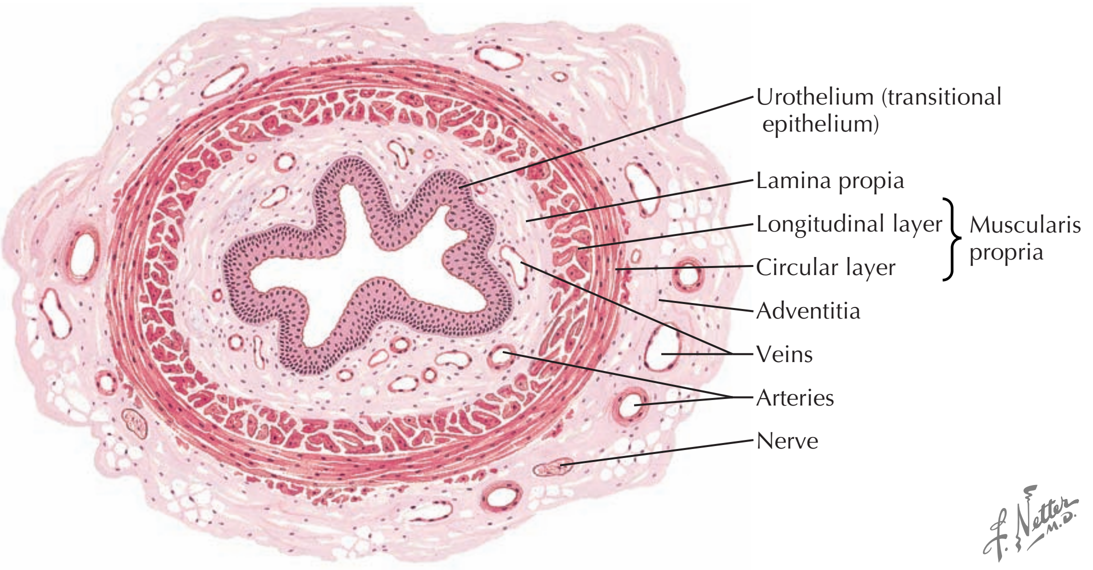
OUTER AND INNER MEDULLARY COLLECTING DUCT

The outer medullary collecting duct (OMCD) consists of principal cells and a smaller population of type A intercalated cells. Both appear taller and less dense than their equivalents in the cortical segment.

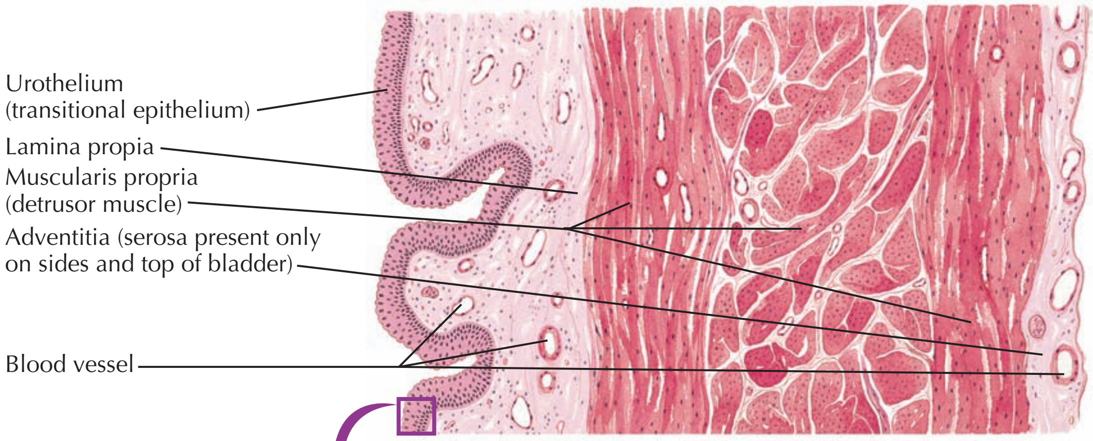
The inner medullary collecting duct (IMCD) is often subdivided into initial and terminal segments. The initial segment contains principal cells that appear similar to those in the OMCD. The terminal segment contains IMCD cells, which resemble principal cells but are taller and have denser microvilli, a lighter staining cytoplasm, and fewer basal invaginations. Both IMCD segments lack intercalated cells.

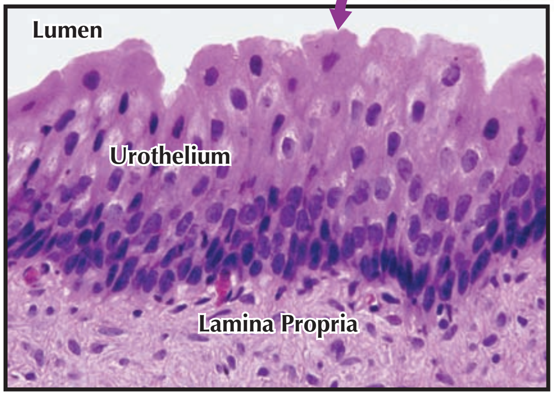
RENAL PELVIS, URETER, AND BLADDER

Section through ureter

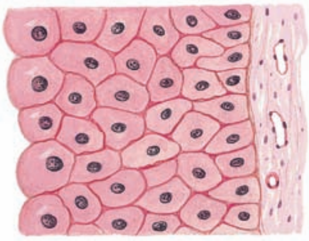


Section through wall of urinary bladder

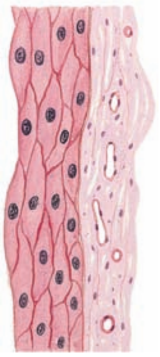

Urothelium (transitional epithelium)
Lamina propia
Muscularis propria (detrusor muscle)
Adventitia (serosa present only on sides and top of bladder)
Blood vessel



Light microscopy. *From Ovalle W, Nahirney P. Netter's Essential Histology, Philadelphia, Saunders, 2008. page 375.*



Urothelium in empty bladder



Urothelium in distended bladder

RENAL PELVIS

The entire urine collecting system is lined by a sheet of transitional epithelium known as urothelium. In the renal pelvis, the urothelial cells are two or three layers thick. The most superficial cells are larger than the others and send projections down over the lateral surfaces of the cells beneath them, sometimes having an umbrella-like appearance. These "umbrella cells" have abundant eosinophilic cytoplasm and may be binucleate. Underneath the umbrella cells are smaller intermediate cells and basal cells.

From the minor calyces onward, these cells rest on top of a thin lamina propria, dual muscle layer, and adventitia. The outer of the two muscular layers consists of "typical" smooth muscle cells, which increase in number near the ureteropelvic junction and extend into the ureter. The inner layer, in contrast, contains "atypical" smooth muscle cells that terminate at the ureteropelvic junction. At present these atypical cells are thought to be the pacemaker cells responsible for the initiation of peristalsis. They are smaller than typical cells and their contractile filaments, instead of running parallel, appear randomly scattered, as in cardiac pacemaker cells. Another population of cells, which resembles interstitial cells of Cajal, has recently been identified in the renal calyces of some mammals, but its function is still being determined.

URETER

The ureter contains three to five layers of urothelial cells, which are thrown into folds with a characteristic stellate appearance. These cells sit on a well-developed, loose lamina propria that contains small vessels and nerves. There is no muscularis mucosae.

Outside of the lamina propria is the muscularis propria, which is continuous with the layer of "typical" smooth muscle cells seen in the renal pelvis. Its contractile fibers are loosely arranged and interspersed with connective tissue. In the upper part of the ureter, there is a vague division into inner longitudinal fibers and outer circumferential fibers, although the distinction is often difficult. In the lower half of the ureter, an additional outer ring of longitudinal fibers tends to appear. Because of the urothelial folds and the well-developed longitudinal musculature, sizable calculi may pass through the ureter without injury to the mucosa. The outermost layer of the ureter contains a thick adventitia with longitudinally oriented small blood vessels.

BLADDER

The bladder contains five to eight irregularly folded layers of urothelial cells. An exception occurs at the trigone, where there are generally fewer layers of urothelial cells with a smooth, unfolded arrangement. As the bladder is distended, the urothelial cells flatten out, with the most superficial cells flattening out to such an extent that they become barely visible. During this process, vesicles near the apical surfaces of the cells fuse with the plasma membrane to provide additional surface area.

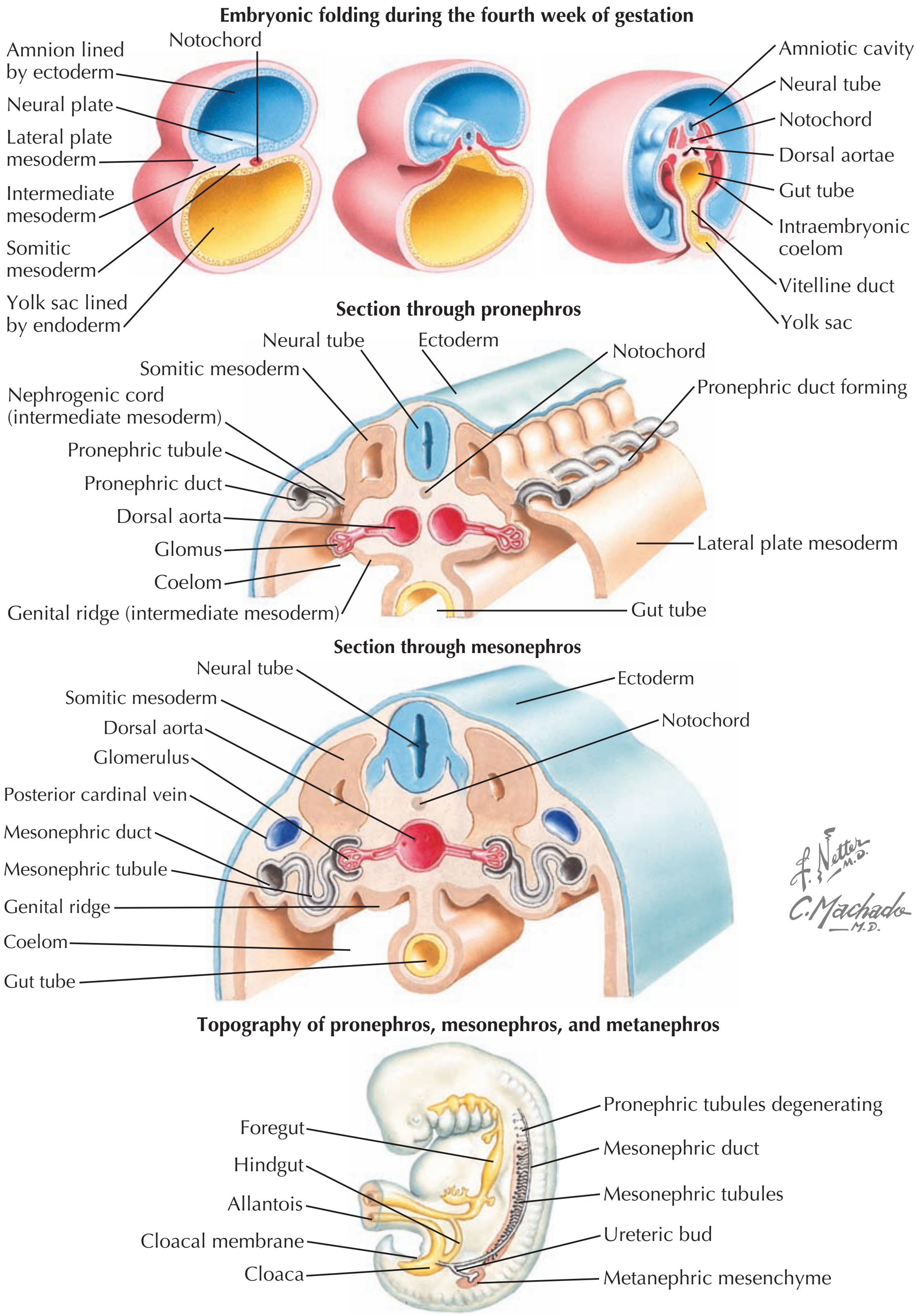
Unlike in the ureter, the lamina propria occasionally contains a muscularis mucosae, which appears discontinuous and contains a haphazard arrangement of wispy, thin bundles of smooth muscle cells. In some instances, the fibers can become hypertrophic and resemble those of the muscularis propria. Uncommonly, adipocytes can be found in the lamina propria.

The muscularis propria is known as the detrusor muscle; as in the lower ureter, it consists of inner and outer longitudinal fibers with an intervening layer of circumferential fibers. Except in the area of the bladder neck, these layers are typically indistinct, appearing as a meshwork of criss-crossed thick muscle bundles. Interspersed through the muscular layers are blood vessels, lymphatics, nerve fibers, and even adipose tissue.

SECTION 2

NORMAL AND ABNORMAL DEVELOPMENT

DEVELOPMENT OF KIDNEY



DEVELOPMENT OF KIDNEY

Embryonic folding during the fourth week of gestation

Amnion lined by ectoderm
Notochord
Neural plate
Lateral plate mesoderm
Intermediate mesoderm
Somitic mesoderm
Yolk sac lined by endoderm
Amniotic cavity
Neural tube
Notochord
Dorsal aortae
Gut tube
Intraembryonic coelom
Vitelline duct
Yolk sac

Section through pronephros

Neural tube
Ectoderm
Somitic mesoderm
Nephrogenic cord (intermediate mesoderm)
Pronephric tubule
Pronephric duct
Dorsal aorta
Glomus
Coelom
Genital ridge (intermediate mesoderm)
Notochord
Pronephric duct forming
Lateral plate mesoderm
Gut tube

Section through mesonephros

Neural tube
Somitic mesoderm
Dorsal aorta
Glomerulus
Posterior cardinal vein
Mesonephric duct
Mesonephric tubule
Genital ridge
Coelom
Gut tube
Ectoderm
Notochord
F. Netter M.D.
C. Machado M.D.

Topography of pronephros, mesonephros, and metanephros

Foregut
Hindgut
Allantois
Cloacal membrane
Cloaca
Pronephric tubules degenerating
Mesonephric duct
Mesonephric tubules
Ureteric bud
Metanephric mesenchyme

The kidneys develop from the intermediate mesoderm, which is located on each side of the embryo between the paraxial (somitic) and lateral plate mesoderm. After the fourth week, during which the embryo undergoes a complex folding process, the intermediate mesoderm forms a lateral nephrogenic cord and a medial genital (gonadal) ridge. The nephrogenic cord gives rise to three successive kidney precursors, while the genital ridge gives rise to the gonads.

The three kidney precursors—known as the pronephros, mesonephros, and metanephros, in order of appearance—develop in a cranial-to-caudal sequence along the nephrogenic cord. Although the pronephros and mesonephros completely regress in utero, they are nonetheless essential for the normal development of the metanephros, which becomes the definitive kidney. The pronephros and mesonephros can be viewed as intermediate structures in the historical evolution of the kidney because they have more important roles in organisms such as fish and amphibians.

Many signaling pathways have been found to play roles in the development of the kidneys, with the already expansive list growing on a regular basis. A detailed discussion of these pathways, however, is beyond the scope of this text, which will instead focus on the anatomic changes that occur during development.

PRONEPHROS

At the start of the fourth week, the cervical portion of the nephrogenic cords undergoes mesenchymal-to-epithelial conversion to form the paired pronephric ducts, which grow in a caudal direction. A series of pronephric tubules appear medial to the ducts and connect them to the coelom, the precursor to the peritoneal space. These tubules constitute the paired pronephroi.

A glomerulus-like structure, known as the glomus, projects from the dorsal aorta into the coelom. The glomus produces filtrate, some of which enters the pronephric tubules and then passes into the pronephric ducts. The pronephric ducts, however, are blind-ended. Thus the pronephroi are not functional excretory organs during human development.

MESONEPHROS

As the paired pronephric ducts continue to grow in a caudal direction, the pronephric tubules degenerate, becoming completely absent by day 25 of gestation. At the same time, however, the growing pronephric ducts continue to grow toward the caudal end of the embryo. These ducts, which become known as the mesonephric (wolffian) ducts, induce the formation of about 40 pairs of mesonephric tubules from the dorsolumbar region of the nephrogenic cords. These tubules constitute the paired mesonephroi.

Each mesonephric tubule receives filtrate from a glomerulus, which receives blood from a branch of the dorsal aorta and drains blood to the posterior cardinal vein. Some tubules drain urine into the mesonephric ducts.

Around the twenty-sixth day of gestation, the mesonephric ducts fuse with the cloaca, the precursor of the urinary bladder. At this point, the mesonephroi become functional excretory organs. The mesonephric tubules degenerate over subsequent months, however, and are almost completely absent by the fourth month of gestation. A small subset, however, persist into adulthood. In males, some of the most caudal tubules form the efferent ductules of the testes. Meanwhile, in females, some of the tubules form vestigial structures known as the epoophoron and paroophoron.

METANEPHROS

The paired metanephroi are the precursors of the definitive adult kidneys. They begin to form around the twenty-eighth day of gestation, shortly after the mesonephric ducts have fused with the cloaca. The caudal portion of each mesonephric duct sprouts a small diverticulum known as a ureteric bud. Each bud then grows toward a nearby mass of mesoderm known as the metanephric mesenchyme, which is located at the sacral end of the ipsilateral nephrogenic cord.

Once each ureteric bud enters its associated metanephric mesenchyme, it begins a process of iterative bifurcation that gives rise to the urine collecting system. The first eight bifurcations of the ureteric bud give rise

Development of Kidney

(Continued)

to the renal pelvis, major calices, and minor calices. These initial divisions later fuse to a considerable extent, resulting in the definitive appearance of the pelvicaliceal system. The next dozen bifurcations give rise to the collecting duct system.

As the collecting ducts are being formed, the surrounding metanephric mesenchyme differentiates into nephrons, each consisting of a glomerulus, proximal tubule, thin limb, distal tubule, and connecting tubule. The ends of these nephrons fuse with the developing collecting duct system. Throughout this process, the ureteric bud and metanephric mesenchyme provide essential inductive signals to one another. Thus, if either one is absent, the metanephros will not develop.

The first phase of nephron formation begins around the sixth or seventh week of gestation. The tips of the branching ureteric buds, known as ampullae, induce the condensation of adjacent mesenchymal cells. Some of the mesenchymal cells form caps over the ampullae, while others form clusters just lateral to the ampullae. The clusters, also known as pretubular aggregates, are the nephron precursors.

Each pretubular aggregate undergoes mesenchymal-to-epithelial conversion to form a hollow vesicle. The proximal end of each vesicle fuses with the adjacent ampulla, the precursor of a collecting duct. Meanwhile, the distal end of each vesicle invaginates to form a cleft, the precursor of Bowman's capsule. The formation and subsequent deepening of the cleft causes the vesicle to become a comma-shaped and then S-shaped body. The cells lining the inner part of the cleft are the precursors of the visceral epithelial cells (podocytes), while those lining the outer part are the precursors of the parietal epithelial cells.

In the S-shaped stage, endothelial cells appear within the cleft and become flattened and fenestrated. The developing podocytes send foot processes over the endothelial cells, and the podocyte basement membrane fuses with that of the endothelial cells, forming the three-layered glomerular basement membrane. Mesangial cell precursors, derived from the metanephric mesenchyme, enter the cleft and form the scaffolding for the developing glomerular capillaries. Throughout this process, the entire primitive nephron lengthens, giving rise to distinct proximal and distal segments.

The second phase of nephron formation begins at approximately the fourteenth week of gestation. During this phase, the ampullae grow outward toward the cortex without further division. As nephrons form adjacent to the growing ampullae in the manner described previously, older nephrons attach to the connecting tubules of newer nephrons rather than directly to the ampullae. This process gives rise to nephron arcades, all joined by a single connecting tubule to a collecting duct. These nephrons become the long-looped (juxtamedullary) nephrons in the mature kidney.

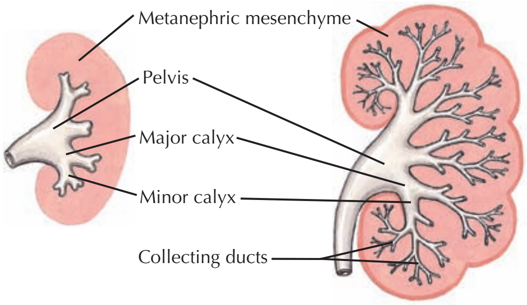
The third phase of nephron formation begins at approximately the twentieth week of gestation. During this phase, the ampullae continue to grow toward the cortex without further division; however, as new nephrons are formed, they retain their individual attachments to the collecting duct system. These nephrons become the short-looped (cortical) nephrons in the mature kidney.

After the thirty-sixth week of gestation, no new nephrons form, but the existing nephrons continue to undergo structural changes. For example, portions of the proximal and distal tubules become increasingly tortuous and convoluted, while the loops of Henle grow deeper into the medulla.

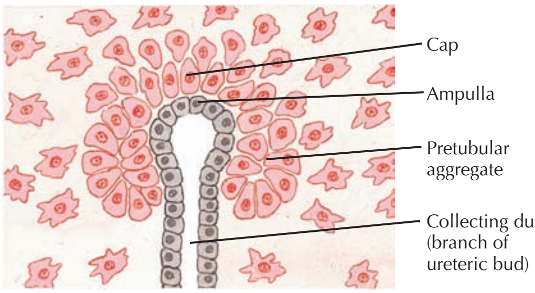
The metanephroi begin to produce urine at 9 weeks of gestation, even as active nephrogenesis is ongoing. Such urination becomes essential for maintaining a normal volume of amniotic fluid. The placenta, however, is the organ responsible for removing waste products from the fetus.

The fetal kidney has a lobated surface appearance, which can be attributed to condensations of metanephric mesenchyme around the initial branches of the ureteric buds. This surface lobation, however, usually disappears around 4 or 5 years of age, as additional tissue fills in the sulcated areas. If fetal lobation persists into adulthood, it is an inconsequential anatomic variant; however, such lobations may be sometimes mistaken for cortical scarring.

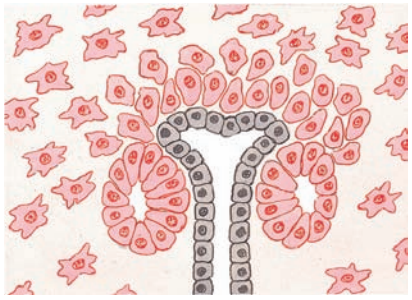
Nephron Formation



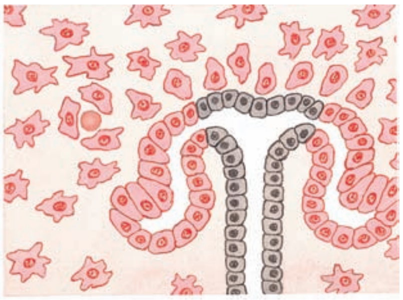
1. After entering the metanephric mesenchyme, the ureteric bud undergoes iterative branching to form the collecting system. Fusion of the initial divisions gives rise to the pelvis and calices.



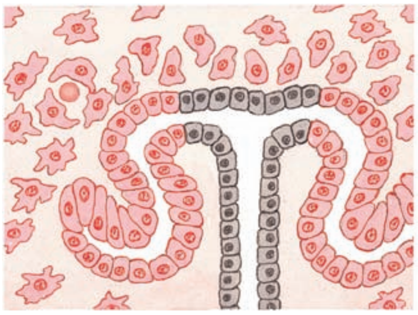
2. After multiple divisions of the ureteric bud, nephrogenesis begins. Each ampulla induces the adjacent metanephric mesenchyme to form caps and pretubular aggregates.



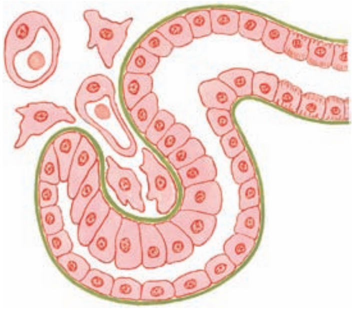
3. The cells of the pretubular aggregates undergo mesenchymal-to-epithelial conversion to form hollow vesicles alongside the branching ampulla.



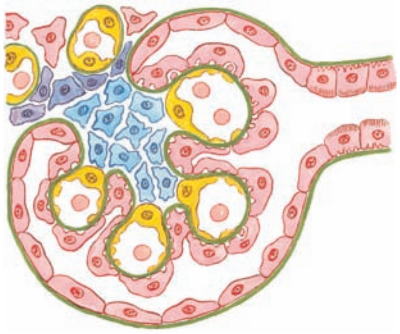
4. The proximal end of each vesicle attaches to the ampulla, while the distal end invaginates to form a cleft. As a result, the vesicle becomes comma shaped.



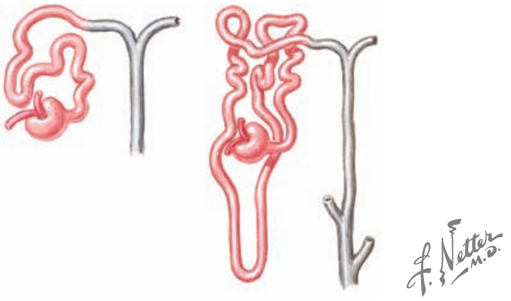
5. Deepening of the cleft results in an S shape. The cleft is the precursor of Bowman's capsule.



6. Endothelial cells appear within the cleft. Meanwhile, a continuous basement membrane develops over the S-shaped body and adjoining ampulla.



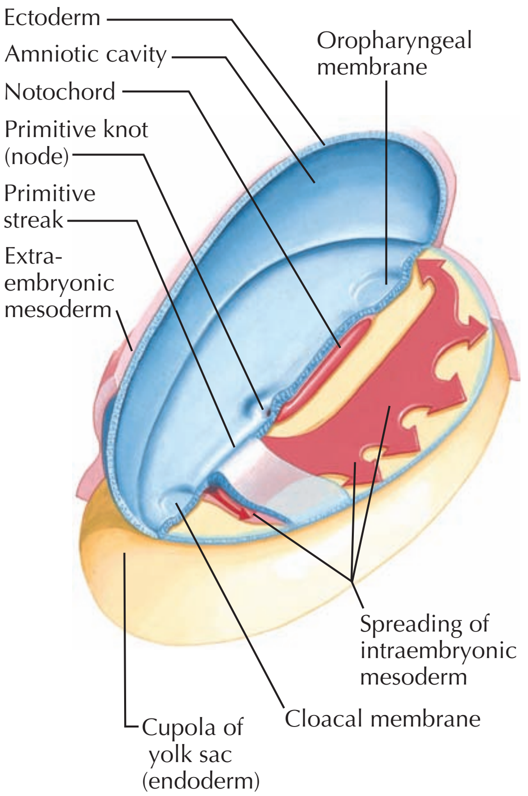
7. The epithelial cells along the inner lining of the cleft become visceral epithelial cells (podocytes), while those on the outer lining become parietal epithelial cells. Mesangial cells form from the mesenchyme.



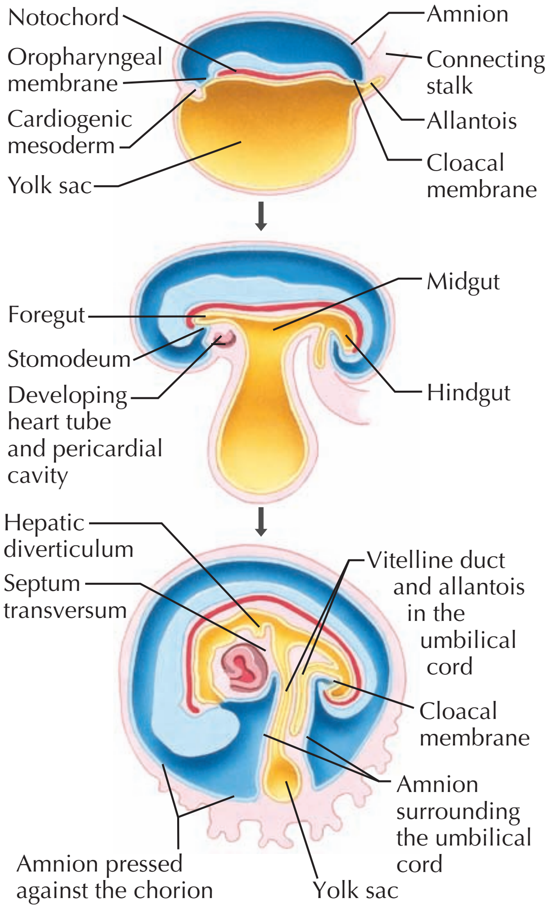
8. The nephron lengthens and undergoes further structural refinements to assume its final, mature form.

FORMATION OF CLOACA

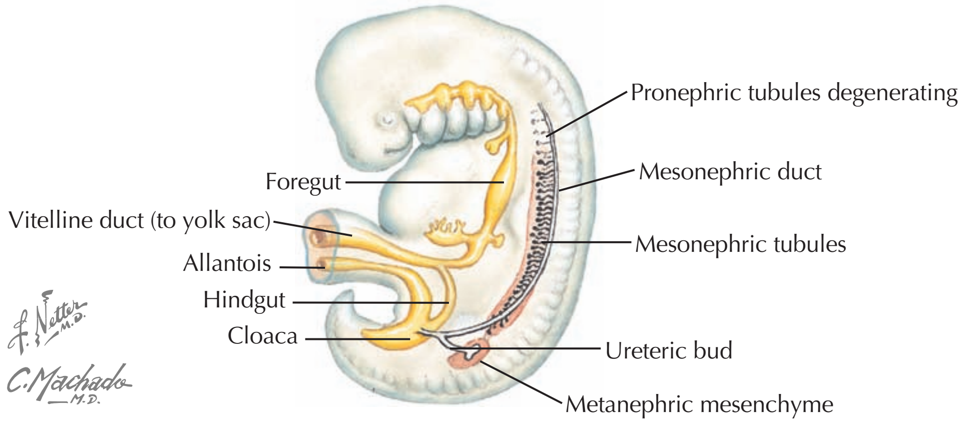
Formation of the cloacal membrane during the third week of gestation


Ectoderm
Amniotic cavity
Notochord
Primitive knot (node)
Primitive streak
Extra-embryonic mesoderm
Oropharyngeal membrane
Spreading of intraembryonic mesoderm
Cloacal membrane
Cupola of yolk sac (endoderm)

Midsagittal section of folding gastrula


Notochord
Amnion
Oropharyngeal membrane
Connecting stalk
Cardiogenic mesoderm
Allantois
Yolk sac
Cloacal membrane
Midgut
Foregut
Stomodeum
Hindgut
Developing heart tube and pericardial cavity
Hepatic diverticulum
Vitelline duct and allantois in the umbilical cord
Septum transversum
Cloacal membrane
Amnion surrounding the umbilical cord
Amnion pressed against the chorion
Yolk sac

Formation of the cloaca from dilation of the terminal hindgut


Pronephric tubules degenerating
Foregut
Mesonephric duct
Vitelline duct (to yolk sac)
Mesonephric tubules
Allantois
Hindgut
Cloaca
Ureteric bud
Metanephric mesenchyme

DEVELOPMENT OF BLADDER AND URETER

FORMATION OF THE CLOACA

The urinary bladder develops from the cloaca, a primitive pouch that forms during the fourth week of gestation. At the beginning of the fourth week, the embryo remains a trilaminar structure consisting of ectoderm, mesoderm, and endoderm. The cloaca has not yet developed, but the cloacal membrane is visible as a small depression near the caudal end of the embryo. At this site, ectoderm from the neural plate merges with endoderm from the yolk sac, without an intervening layer of mesoderm.

During the fourth week the embryo undergoes a folding process, during which the yolk sac gives rise to the gut tube. The caudal part of the gut tube, known as the hindgut, terminates at the cloacal membrane. The most caudal end of the hindgut dilates to form the cloaca.

The cranioventral aspect of the cloaca is continuous with a narrow tube, known as the allantois, that extends into the connecting stalk. Meanwhile, the lateral walls of the cloaca receive the mesonephric (wolffian) ducts.

SEPTATION OF THE CLOACA

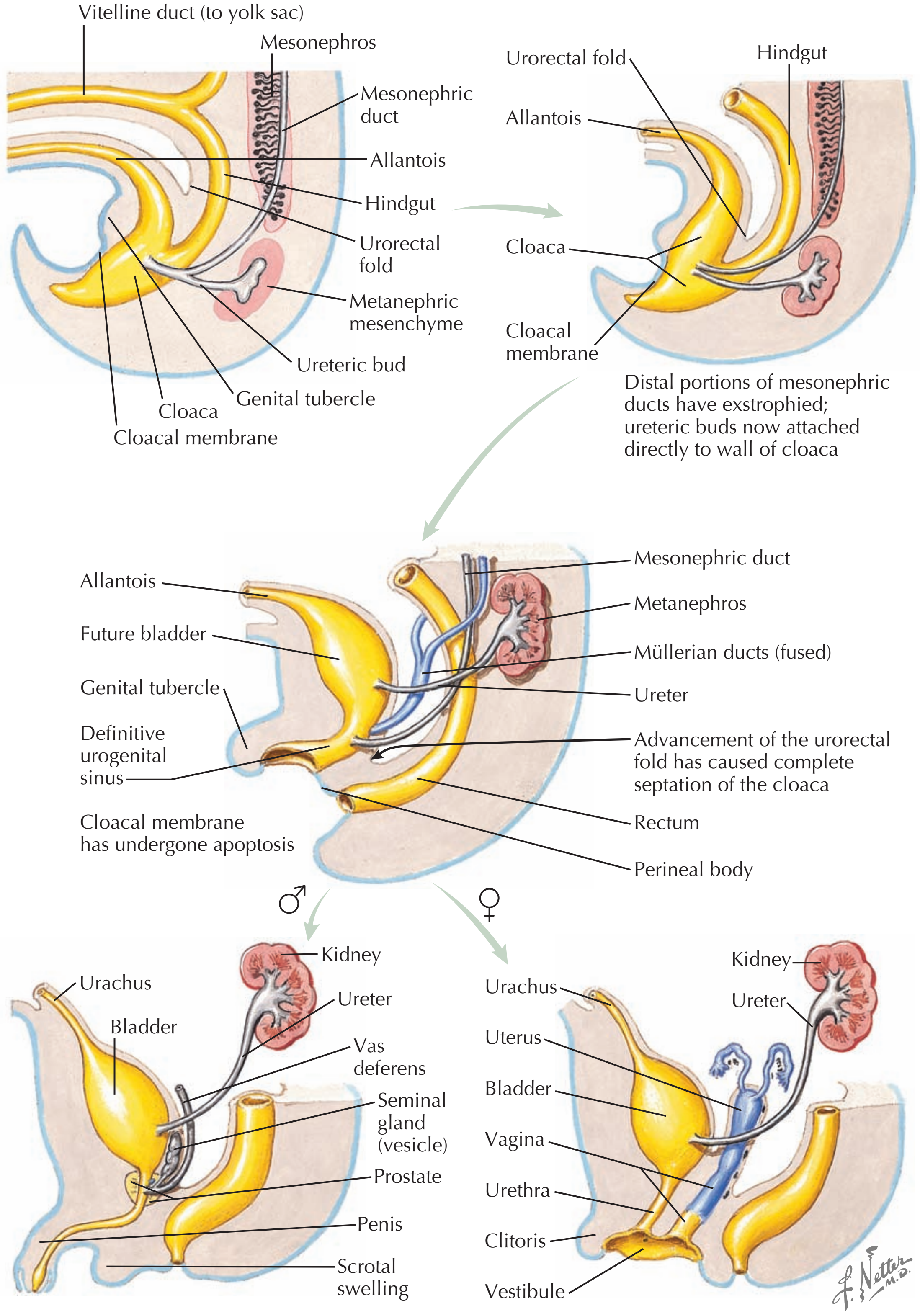
By the sixth week, a septum divides the cloaca into an anterior primitive urogenital sinus and posterior rectum. The exact mechanism of the septation process has long been a topic of active debate and investigation. Some have proposed that a septum oriented in the coronal plane descends through the cloaca in a cranial-to-caudal direction, while others have proposed that two lateral cloacal folds fuse in the midline to form a septum. Still others have proposed various combinations of the two previous theories. More recent investigations have rejected both of these theories, instead arguing that septation results from advancement of the dorsal cloaca toward the cloacal membrane as the embryo lengthens and rotates. During this process, the urorectal fold, located between the allantois and the hindgut, passively advances toward the cloacal membrane, causing effective septation. Subsequent apoptosis of the cloacal membrane establishes two distinct openings that lead to the primitive urogenital sinus and rectum. The tip of the septum lying between them gives rise to the perineal body.

MATURATION OF THE BLADDER

After cloacal septation is complete, the primitive urogenital sinus contains three major parts. The most caudal part is known as the definitive urogenital sinus, and it will become the penile and spongy urethra in males, or the vestibule of the vagina in females. The neck, located just proximal to the definitive urogenital sinus, will become the membranous and prostatic urethra in males, or the urethra in females. The bulging area proximal to the neck will become the urinary bladder in both sexes. The allantois, which connects the bladder to the umbilical cord, will regress to form the a thick, epithelial-lined tube known as the urachus, which in turn will further degenerate into a simple fibrous cord known as the median umbilical ligament.

During subsequent weeks, the definitive urogenital sinus continues to undergo structural changes as it

SEPTATION, INCORPORATION OF URETERS, AND MATURATION


Vitelline duct (to yolk sac)
Mesonephros
Mesonephric duct
Allantois
Hindgut
Urorectal fold
Metanephric mesenchyme
Ureteric bud
Genital tubercle
Cloaca
Cloacal membrane
Urorectal fold
Hindgut
Allantois
Cloaca
Cloacal membrane
Allantois
Future bladder
Genital tubercle
Definitive urogenital sinus
Cloacal membrane has undergone apoptosis
Mesonephric duct
Metanephros
Müllerian ducts (fused)
Ureter
Rectum
Perineal body
♂
♀
Urachus
Bladder
Kidney
Ureter
Vas deferens
Seminal gland (vesicle)
Prostate
Penis
Scrotal swelling
Urachus
Uterus
Bladder
Vagina
Urethra
Clitoris
Vestibule
Kidney
Ureter

Distal portions of mesonephric ducts have exstrophied; ureteric buds now attached directly to wall of cloaca

Advancement of the urorectal fold has caused complete septation of the cloaca

DEVELOPMENT OF BLADDER AND URETER *(Continued)*

becomes the mature bladder. By the tenth week, the endodermal cells become a single layer of cuboidal epithelium. Over subsequent weeks, additional cell layers appear, which begin to assume the characteristics of differentiated urothelial cells. Meanwhile, during the twelfth week, the surrounding splanchnopleuric mesoderm differentiates to form the detrusor muscle, which lines the urothelium. As bladder development proceeds, the mechanical distention associated with urine storage appears to be essential for the development of normal wall compliance.

MATURATION OF THE URETERS

The ureteric buds appear during the fifth week of gestation as small diverticula near the caudal ends of the mesonephric ducts (see Plate 2-1). They eventually give rise to the ureters, renal pelves, calices, and collecting ducts.

Although the ureteric buds originally drain into the mesonephric ducts, they are transferred to the future bladder in a process known as mesonephric duct exstrophy, which occurs during cloacal septation. In this process, the most caudal ends of the mesonephric ducts evert and balloon into the lumen of the urogenital sinus. Eventually, the eversion of each duct is extensive enough to bring the attached ureteric bud into the sinus. The buds then separate from the mesonephric ducts and fuse with the posterior wall of the urogenital sinus.

A ureteric bud with a more caudal position on the mesonephric duct will not be drawn far into the bladder during the exstrophy process, resulting in a more superior and lateral ureteric orifice, as well as a short course through the bladder wall. In contrast, a ureteric bud with a more cranial position on the mesonephric duct will be drawn deep into the bladder, resulting in a more inferior and medial ureteric orifice, as well as a longer intramural course.

Like the bladder, each ureter develops from a simple epithelial tube into a complex, multilayered structure containing urothelium, smooth muscle, and connective tissue. There is transient obliteration of the ureteral lumen during the sixth week of gestation. Recanalization quickly ensues, however, starting in the midureter region and progressing in both directions until the entire lumen is once again patent.

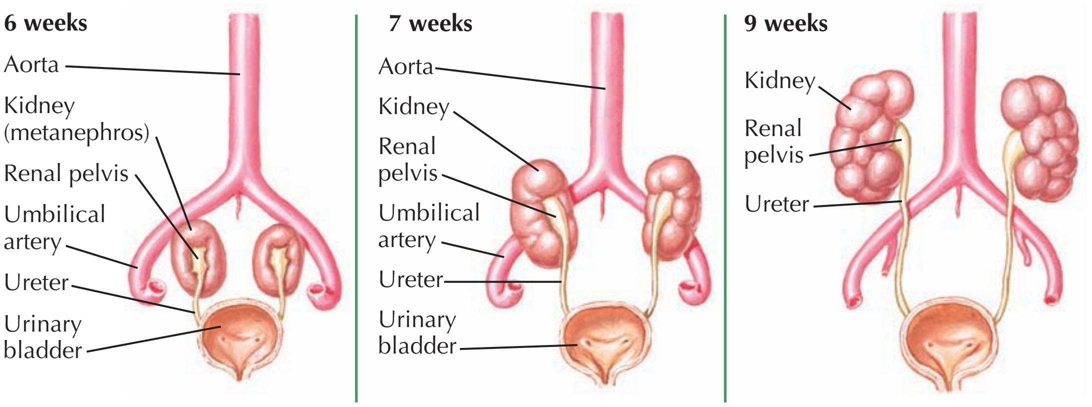
FATE OF THE MESONEPHRIC DUCTS

By the end of the exstrophy process, the mesonephric ducts terminate in the bladder medial and inferior to the future ureteric orifices. Although it was previously thought that the mesonephric ducts contributed to the formation of the trigone, this long-held view has recently been called into doubt.

In males, the mesonephric ducts become the ejaculatory ducts, vas deferens, seminal glands (vesicles), and epididymis. In females, in contrast, the mesonephric ducts largely degenerate, giving rise only to the vestigial structures known as the epoöphoron and paroöphoron. Instead, the paramesonephric (müllerian) ducts, which degenerate in males, are responsible for formation of the female reproductive tract. These ducts appear lateral to the mesonephric ducts during the sixth week, and in females they become the uterine (fallopian) tubes, uterus, and upper two thirds of the vagina.

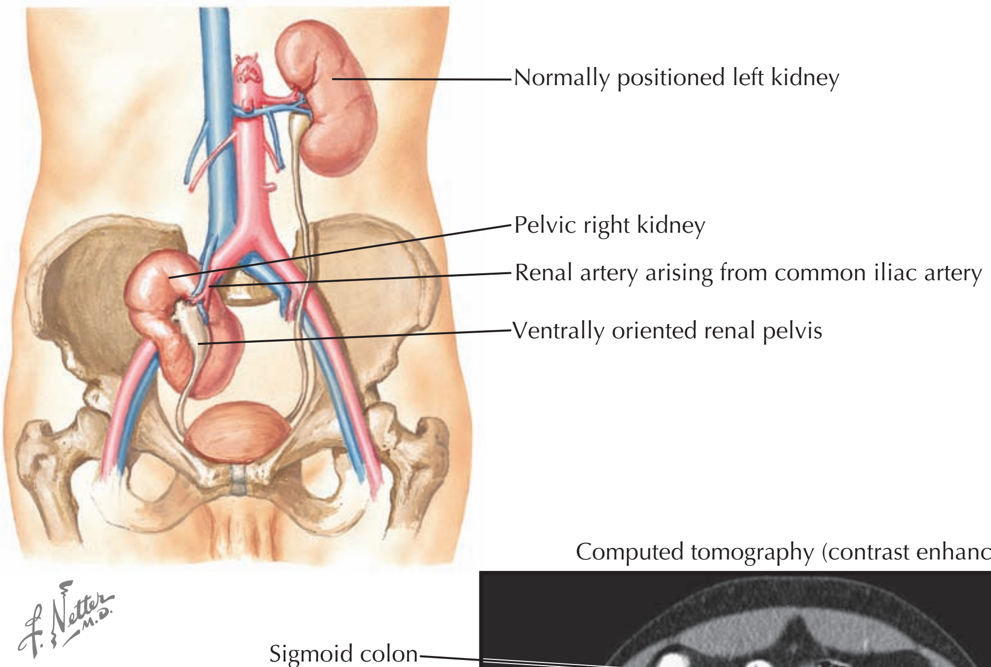
NORMAL RENAL ASCENT AND PELVIC KIDNEY

Normal ascent

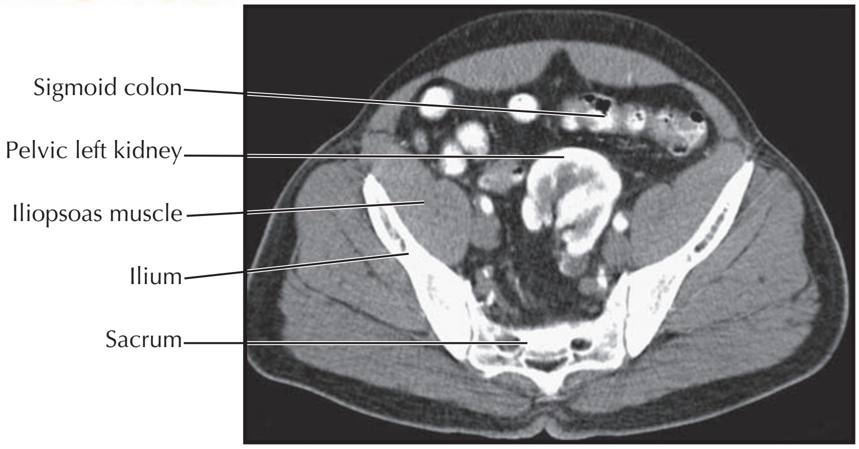

6 weeks
Aorta
Kidney (metanephros)
Renal pelvis
Umbilical artery
Ureter
Urinary bladder
7 weeks
Aorta
Kidney
Renal pelvis
Umbilical artery
Ureter
Urinary bladder
9 weeks
Kidney
Renal pelvis
Ureter

A series of transient branches from the aorta, not shown here, serve as renal vessels during the process of ascent. The final pair become the definitive renal arteries.

Pelvic kidney


Normally positioned left kidney
Pelvic right kidney
Renal artery arising from common iliac artery
Ventrally oriented renal pelvis

Computed tomography (contrast enhanced)


Sigmoid colon
Pelvic left kidney
Iliopsoas muscle
Ilium
Sacrum

RENAL ASCENT AND ECTOPIA

NORMAL RENAL ASCENT

The adult kidneys are positioned in the lumbar retroperitoneum; however, their development begins in the sacral region of the fetus, where the paired metanephroi appear during the fifth week of development. Their change in position reflects a process known as renal ascent, which occurs during the sixth to ninth weeks of gestation. Although its exact mechanism is not well understood, it likely reflects rapid growth of the sacral end of the fetus, which leads to a change in the relative position of the kidneys.

As they ascend, the kidneys are vascularized by a series of transient branches from the dorsal aorta. In most individuals, all but the final pair of arterial branches degenerate, leaving one major renal artery extending to each kidney. In some individuals, however, the earlier branches of the aorta may fail to degenerate, resulting in aberrant persistence of an extrahilar (polar) artery. (This condition is so common that it is considered a normal anatomic variant, rather than a congenital defect, and is thus described in more detail in the section on normal renal vasculature. See Plate 1-12.)

RENAL ECTOPIA

Renal ectopia results from abnormalities during the process of ascent. If a kidney fails to ascend at all, it is known as a pelvic kidney. If it undergoes incomplete ascent, it is known as a lumbar kidney. If it ascends too far and reaches the thorax, it is known as a thoracic kidney. Finally, if a kidney ascends to the contralateral side, it is known as a crossed ectopic kidney.

Pelvic Kidney. Pelvic kidney is the most common form of renal ectopia, with an estimated incidence of 1 in 2,200 to 3,000. A common view is that this pattern of ectopia represents persistence of fetal vasculature, which prevents the normal ascent of the kidney. Other possible causes, however, encompass intrinsic defects in the ureteric bed or metanephric mesenchyme.

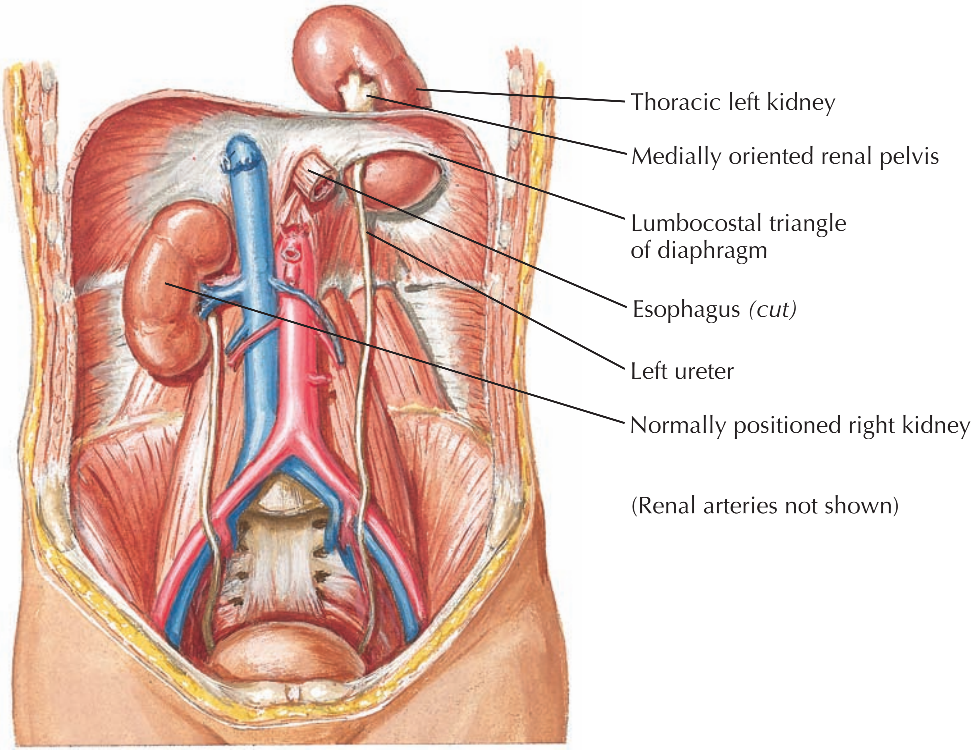
The vessels that supply a pelvic kidney typically arise from the iliac vessels or the most inferior portion of the abdominal aorta. The ureter is short and often prone to reflux. The hilum may be directed ventrally, rather than medially, because of a failure of normal rotation (see Plate 2-7).

Most patients with pelvic kidneys are asymptomatic, and the abnormality is either incidentally noted or never discovered. A subset of individuals, however, may become symptomatic secondary to the development of an upper urinary tract obstruction, nephrolithiasis, or urinary tract infection. These sequelae occur if malrotation results in high insertion of the ureter or a vessel crossing the collecting system, since these can both cause urinary stasis and outflow obstruction.

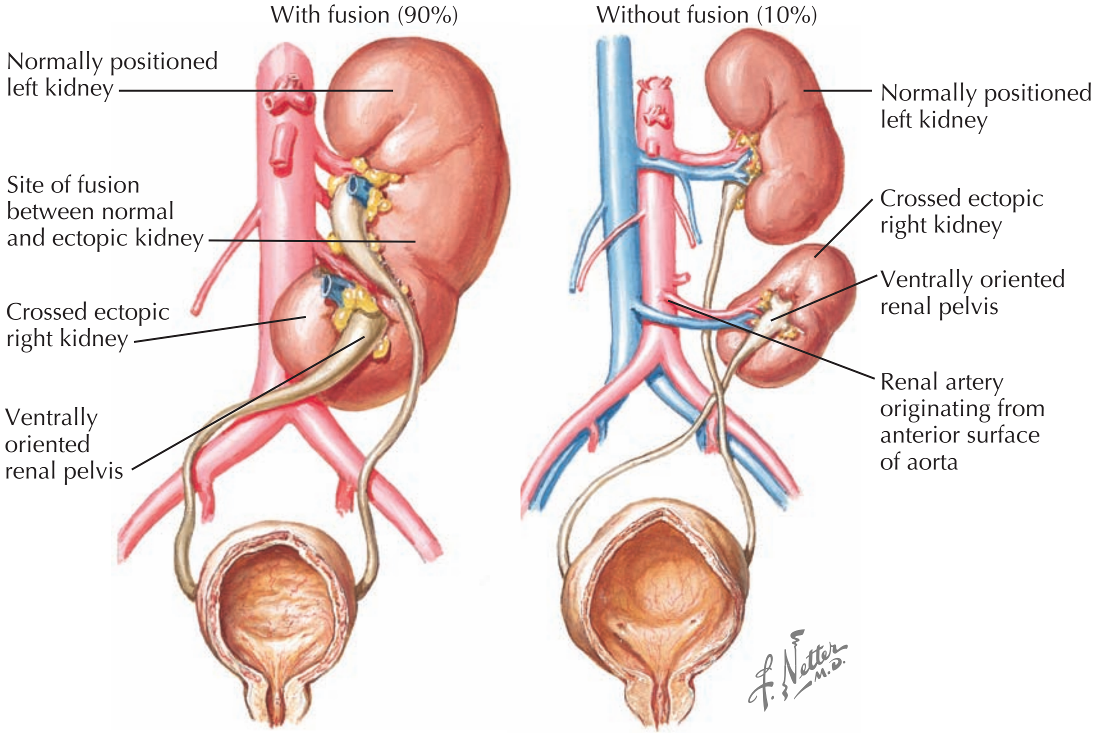
Thus, patients with pelvic kidneys may occasionally have abdominal pain, hematuria, or a palpable abdominal mass. The pelvic kidney is then detected on further workup with ultrasound or computed tomography (CT). The treatment strategies for nephrolithiasis and ureteropelvic junction obstructions in patients with pelvic kidneys are largely the same as those used for patients with normally positioned kidneys; however, the abnormal course of the ureter may make ureteroscopy

THORACIC AND CROSSED ECTOPIC KIDNEY

Thoracic kidney


Thoracic left kidney
Medially oriented renal pelvis
Lumbocostal triangle of diaphragm
Esophagus (cut)
Left ureter
Normally positioned right kidney
(Renal arteries not shown)

Crossed renal ectopia


With fusion (90%)
Without fusion (10%)
Normally positioned left kidney
Site of fusion between normal and ectopic kidney
Crossed ectopic right kidney
Ventrally oriented renal pelvis
Normally positioned left kidney
Crossed ectopic right kidney
Ventrally oriented renal pelvis
Renal artery originating from anterior surface of aorta
F. Netter M.D.

RENAL ASCENT AND ECTOPIA

(Continued)

difficult, and there is a risk of damaging abnormally positioned vessels and nerves.

A pelvic kidney is more susceptible to injury from blunt trauma than a normally positioned kidney because the latter is (1) surrounded by a large, protective cushion of perinephric and retroperitoneal fat, (2) protected posteriorly by the ribs, and (3) located at a safe distance from the anterior abdominal wall and narrow pelvis. As a result, patients known to have pelvic kidneys should be encouraged to wear appropriate protection if they participate in contact sports.

Thoracic Kidney. Thoracic kidney is the rarest form of all renal ectopias, with an estimated incidence of 1 in 13,000 according to one autopsy series. Unlike pelvic kidneys, thoracic kidneys appear to be more common in males. An ectopic thoracic kidney may be located predominantly above or below the diaphragm. In either case, the intrathoracic portion passes through the lumbocostal triangle (foramen of Bochdalek) and is covered by a thin membrane of the diaphragm. As a result, the kidney does not reside within the pleural space; however, the adjacent region of the lung may be hypoplastic. Thoracic kidneys are more commonly seen on the left side, possibly because the liver blocks excessive ascent of the right kidney.

It is unclear why thoracic kidneys occur, but two possibilities include delayed closure of the diaphragm, as well as excessive and accelerated renal ascent.

The vessels that supply a thoracic kidney usually arise from the abdominal aorta at a higher position than normal. The ureter is appropriately increased in length and inserts normally into the bladder. Renal rotation is usually complete, and thus the renal pelvis has a normal medial orientation. Both the ureter and renal vessels pass through the lumbocostal triangle as they course from the kidney to the abdomen. The associated adrenal gland typically remains in its normal position but has been documented in some cases to be associated with the ectopic kidney.

Most thoracic kidneys are asymptomatic, causing neither respiratory nor urinary symptoms. Thus this abnormality often goes undetected unless a patient undergoes imaging for another unrelated reason.

Crossed Renal Ectopia. Crossed ectopia of the kidney is an uncommon condition in which one or both kidneys are found on the contralateral side of the abdomen. The "crossing" of a kidney is evidenced by the path of its associated ureter, which crosses the midline to insert into the opposite side of the bladder.

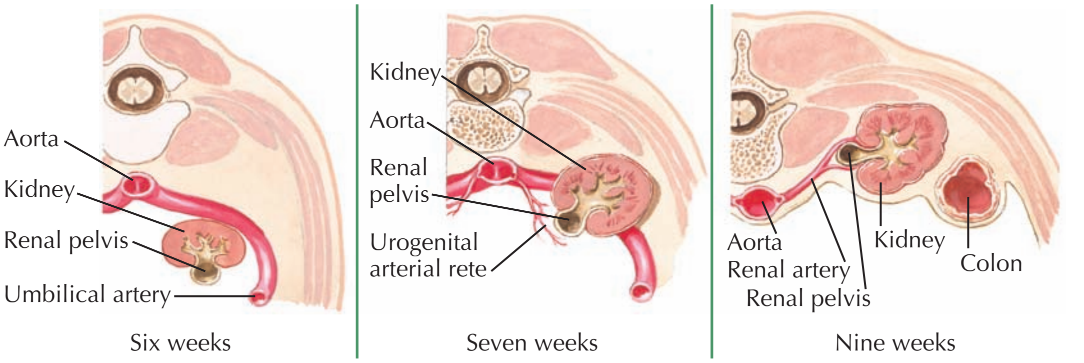
The embryologic basis for crossed renal ectopia is not known. It has been speculated that during renal development, the ureteric bud may cross the midline to enter the contralateral metanephric mesenchyme. Others have suggested that abnormally positioned vessels, such as the umbilical artery, may obstruct the normal path of an ascending kidney, which then takes the path of least resistance to the contralateral side. Teratogens or genetic factors may also play a role.

The crossed kidney generally lies caudal to the normally positioned kidney and has a ventrally oriented renal pelvis. In 90% of cases, the crossed kidney is fused with the inferior pole of the normally positioned kidney. In about 10% of cases, the two kidneys remain separate and distinct. The renal artery of the ectopic kidney may originate from the iliac artery or from either the lateral or anterior surfaces of the abdominal aorta.

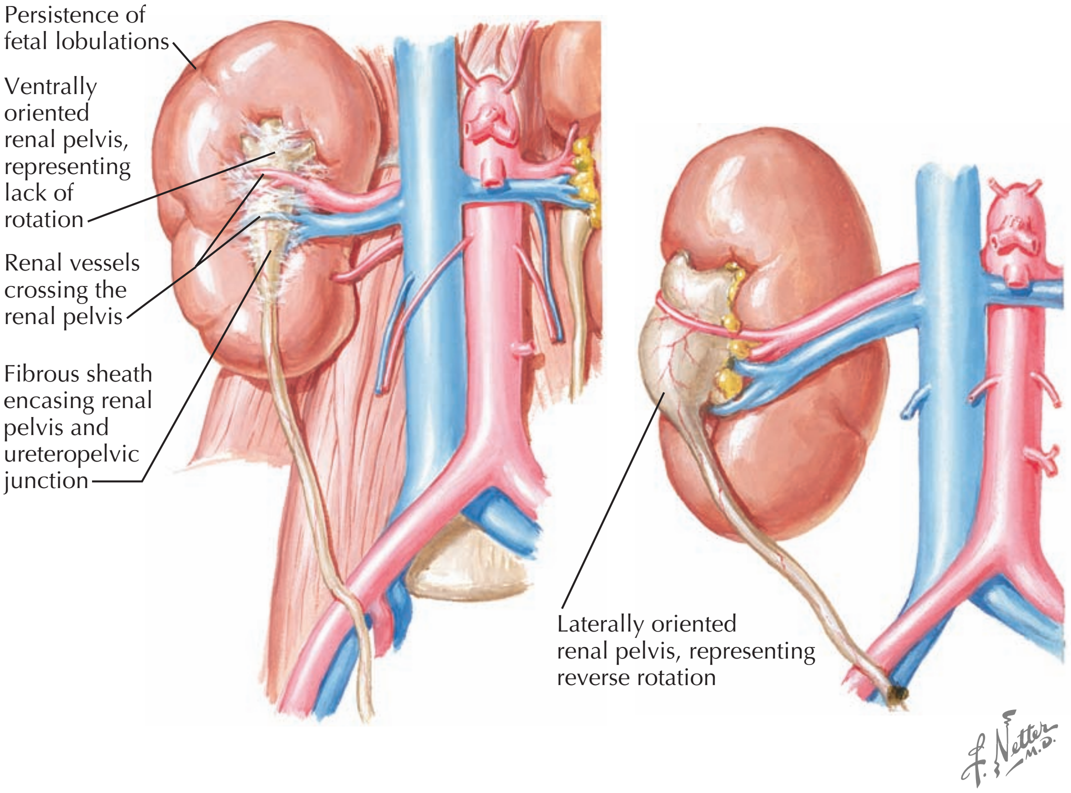
Like pelvic kidneys, crossed ectopic kidneys are usually incidental, asymptomatic findings but may rarely occur with abdominal pain, hematuria, or other symptoms.

RENAL ROTATION AND MALROTATION

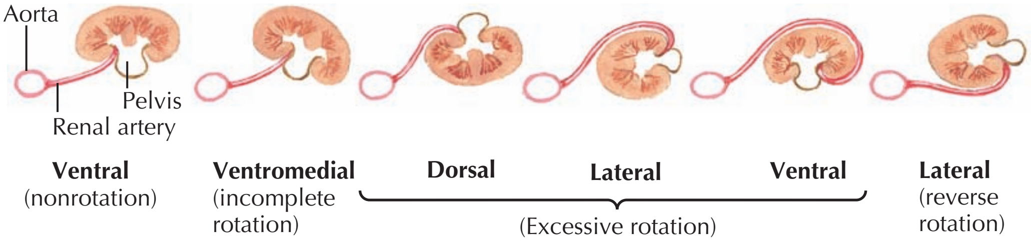
Normal rotation (axial view)


Aorta
Kidney
Renal pelvis
Umbilical artery
Six weeks
Kidney
Aorta
Renal pelvis
Urogenital arterial rete
Seven weeks
Aorta
Renal artery
Renal pelvis
Kidney
Colon
Nine weeks

Malrotation


Persistence of fetal lobulations
Ventrally oriented renal pelvis, representing lack of rotation
Renal vessels crossing the renal pelvis
Fibrous sheath encasing renal pelvis and ureteropelvic junction
Laterally oriented renal pelvis, representing reverse rotation
F. Netter M.D.

Possible configurations


Aorta
Pelvis
Renal artery
Ventral (nonrotation)
Ventromedial (incomplete rotation)
Dorsal
Lateral
Ventral
(Excessive rotation)
Lateral (reverse rotation)

NORMAL RENAL ROTATION

During their normal process of ascent (see Plate 2-5), the kidneys undergo 90 degrees of medial rotation, such that the renal pelvis is reoriented from its original ventral position to a final medial position. The mechanism of normal renal rotation is unknown but has been hypothesized to represent asymmetric branching of the ureteric bud in the metanephric mesenchyme. With an increased number of ventrolateral rather than dorsomedial ureteric bud branches, the metanephric mesenchyme would preferentially differentiate in a manner that could cause the appearance of rotation.

RENAL MALROTATION

Renal malrotation is a rare phenomenon that may occur either in isolation or, more commonly, in combination with renal ectopia (see Plates 2-5 and 2-6). The true incidence is not well-characterized but, based on previous reports, is likely in the range of 1:500 to 1:1500 with an increased propensity among males.

It is unclear if renal malrotation represents abnormalities in the asymmetric branching process thought to underpin normal rotation, or whether it results from other factors. For example, it has been hypothesized that malrotation may occur if the ureteric bud inserts into an abnormal region of the metanephric mesenchyme. The association with renal ectopia suggests that certain processes may interrupt both normal ascent and rotation, or that ascent itself is important in some way for the normal process of rotation to occur.

In most cases of malrotation, the kidney fails to rotate at all, leaving the renal pelvis facing ventrally. Less frequently, the kidney may be only partially rotated, excessively rotated, or rotated in the wrong direction. Because the renal vessels are not believed to be responsible for malrotation, but rather twist around the kidneys as they rotate, their course offers a clue into the direction and degree of malrotation. For example, a kidney with a laterally directed renal pelvis may have undergone either 270 degrees of medial rotation or 90 degrees of lateral rotation. Likewise, a kidney with an ventrally directed renal pelvis may have undergone either no rotation at all or 365 degrees of rotation. In these cases, the path of the renal vessels allows one to make the distinction, as shown in the plate.

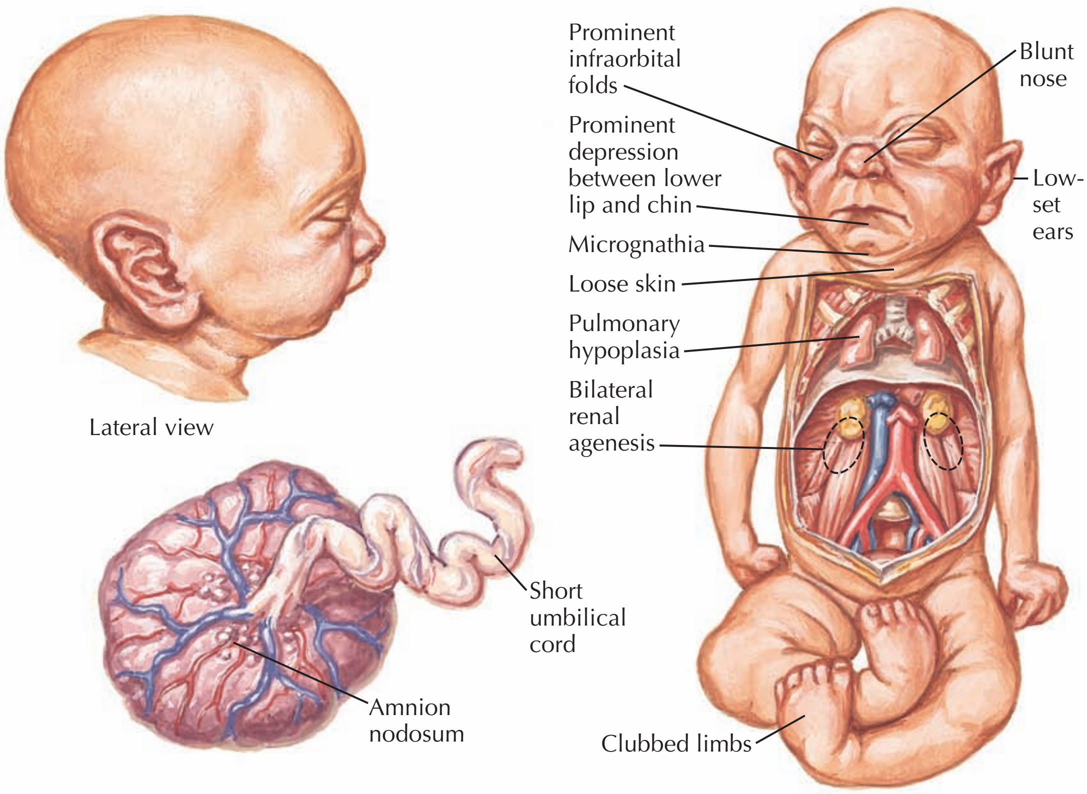
In addition to its association with ectopy, renal malrotation is usually associated with abnormalities in renal structure. For example, fetal lobulations are typically prominent over the gross surface. In addition, the renal pelvis is usually encased with an abnormally thick amount of fibrous tissue.

In most cases, malrotated kidneys cause no symptoms and are discovered only as incidental findings. In rare cases, however, patients may experience symptoms of upper tract obstruction, nephrolithiasis, or urinary tract infection. These occur if there is urinary stasis or outflow obstruction secondary to the fibrous encasing of the renal pelvis, a high insertion of the ureteropelvic junction, or obstruction of the renal pelvis by an overlying renal vessel. Such symptoms usually consist of nonspecific abdominal, flank, or back pain, and/or hematuria. The malrotation is then discovered on radiographic imaging of the abdomen. It is important to rule out the presence of a pelvic mass, which can rotate and displace the kidney from its normal position.

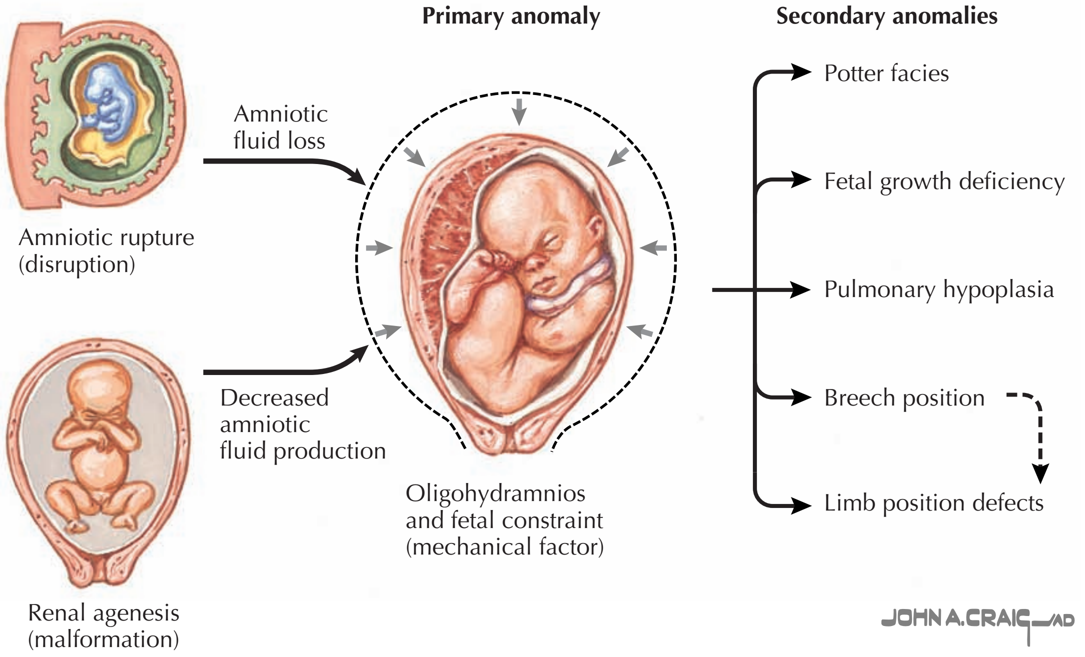
Most malrotated kidneys do not require definitive treatment. If significant symptoms persist, however, or if significant hydronephrosis is present, surgical repair of the renal pelvis and/or ureteropelvic junction may be necessary.

BILATERAL RENAL AGENESIS

Appearance of fetus


Lateral view
Prominent infraorbital folds
Prominent depression between lower lip and chin
Micrognathia
Loose skin
Pulmonary hypoplasia
Bilateral renal agenesis
Blunt nose
Low-set ears
Short umbilical cord
Amnion nodosum
Clubbed limbs

Potter sequence


Primary anomaly
Secondary anomalies
Amniotic rupture (disruption)
Amniotic fluid loss
Renal agenesis (malformation)
Decreased amniotic fluid production
Oligohydramnios and fetal constraint (mechanical factor)
Potter facies
Fetal growth deficiency
Pulmonary hypoplasia
Breech position
Limb position defects
JOHN A.CRAIG AD

ANOMALIES IN NUMBER OF KIDNEYS

RENAL AGENESIS

Renal agenesis is defined as the complete absence of one or both pairs of kidneys and ureters. It represents a failure of the ureteric bud and metanephric mesenchyme to engage in the process of reciprocal induction and differentiation required for metanephros formation. As a result, both the kidney and ureter fail to develop. Renal aplasia, in contrast, occurs when there is abnormal differentiation of the metanephric mesenchyme and ureteric bud that leads to involution of the kidney, but with persistence of a rudimentary collecting system.

Because numerous signaling molecules are involved in normal metanephros development, the range of genetic defects that may cause renal agenesis is vast and under active investigation. Recent evidence, however, suggests a prominent role for abnormalities in the GDNF-RET signaling cascade. GDNF (glial cell line-derived neurotrophic factor) is expressed in the masses of metanephric mesenchyme lying near the mesonephric (wolffian) ducts. It binds to RET, a receptor tyrosine kinase, in the mesonephric ducts and induces formation of the ureteric buds. Mutations in the genes encoding these proteins prevent formation of the ureteric buds and have been noted in fetuses with renal agenesis.

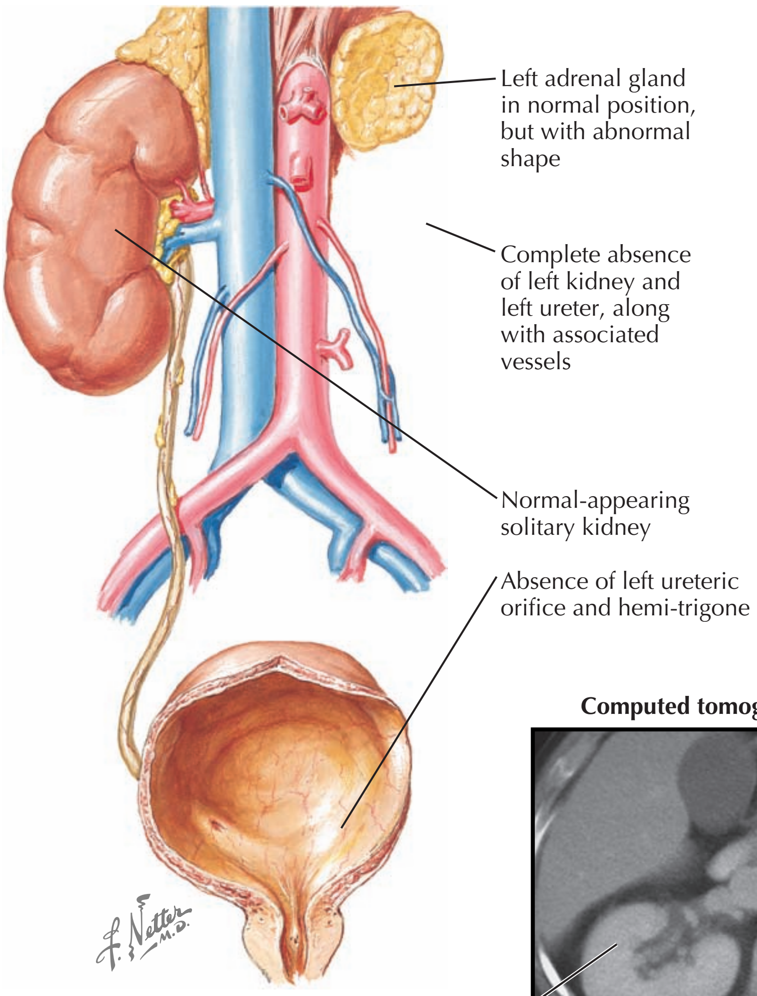
In some cases, male fetuses with renal agenesis still develop normal mesonephric duct derivatives (i.e., the vas deferens, seminal glands [vesicles], and epididymis), indicating that the underlying developmental defect affected only ureteric bud branching or metanephric induction. Fetuses with broader defects, in contrast, have likely sustained insults to the intermediate mesoderm, which gives rise to both the nephrogenic cords and genital ridge (see Plate 2-1).

Bilateral renal agenesis. Bilateral renal agenesis, defined as the complete absence of both kidneys and ureters, is a rare abnormality that occurs in approximately 1 : 5000 to 1 : 10,000 fetuses. Males are affected at least twice as often as females. There is evidence that a significant number of affected fetuses have abnormalities in signaling cascades important to renal development, such as the GDNF-RET pathway described above. A subset of affected fetuses, however, also have associated abnormalities that suggest a more wide-ranging defect in caudal development, such as sirenomelia (fused lower extremities, imperforate anus, renal agenesis, and abnormal or absent genitalia).

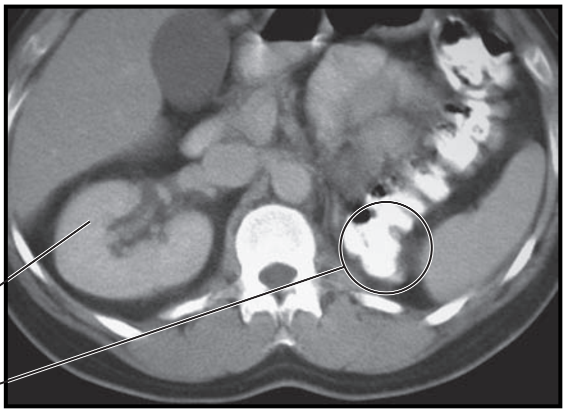
Bilateral renal agenesis is typically diagnosed using prenatal ultrasound. Normally the fetal kidneys can be visualized starting at approximately the twelfth week of gestation. In bilateral renal agenesis, however, no renal parenchyma can be visualized either in the normal renal fossae or other ectopic locations, such as the fetal pelvis or thorax. The fetal adrenal glands are in normal position but may appear less flattened because of the lack of normal compression from the kidneys. Finally, the fetal bladder appears empty, and the normal cycles of filling and emptying are not seen.

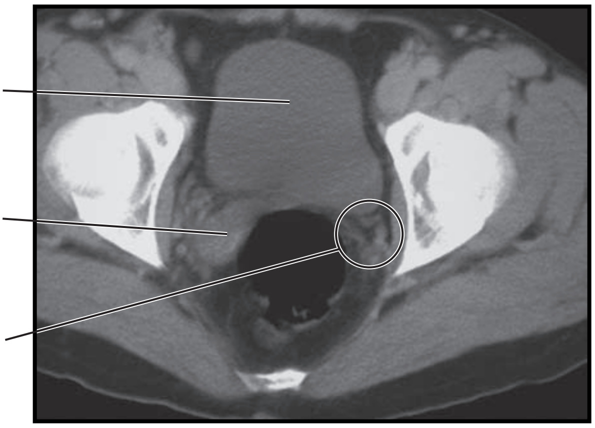
Severe oligohydramnios is a major consequence of bilateral renal agenesis and may be one of the more notable sonographic findings. Before 20 weeks of gestation, diffusion of fluid into the amnion produces

UNILATERAL RENAL AGENESIS


Left adrenal gland in normal position, but with abnormal shape
Complete absence of left kidney and left ureter, along with associated vessels
Normal-appearing solitary kidney
Absence of left ureteric orifice and hemi-trigone
F. Netter M.D.

Computed tomography (contrast enhanced)


Normal-appearing solitary right kidney
Complete absence of left kidney; splenic flexure occupies left renal fossa


Bladder
Right seminal gland (vesicle)
Complete absence of left seminal gland (vesicle)

ANOMALIES IN NUMBER OF KIDNEYS *(Continued)*

a significant fraction of the amniotic fluid, which therefore may appear normal in volume even despite a lack of fetal renal function. After 20 weeks, however, the fetal kidneys are responsible for producing over 90% of the amniotic fluid. Severe oligohydramnios at this stage of development is therefore a very sensitive sign of bilateral agenesis. It is not, however, particularly specific, and other possible causes—including bilateral renal dysplasia, bilateral renal cystic disease, urinary outflow tract obstruction, premature rupture of membranes, and fetal demise—must be ruled out.

Severe oligohydramnios, irrespective of the cause, has numerous adverse effects on the fetus. First, the increase in intrauterine pressure results in physical compression of the growing fetus, which leads to a blunted nose; low-set, flattened ears that appear enlarged; micrognathia; prominent infraorbital folds; a prominent depression between the lower lip and chin; clubbed limbs; and dislocated hips. In addition, the lack of amniotic fluid causes abnormal development of the skin, which appears loose and excessively dry. Finally, the increased pressure on the fetal thorax and decline in circulating amniotic fluid leads to severe pulmonary hypoplasia. The cause-and-effect relationship between oligohydramnios and these various sequelae is known as the Potter sequence.

Bilateral renal agenesis is fatal. Forty percent of affected fetuses die in utero, and the remainder develop severe respiratory distress shortly after birth. Therefore, if the diagnosis is established using prenatal ultrasound, therapeutic abortion is typically recommended. Because most cases of bilateral renal agenesis are sporadic, the risk of recurrence in a subsequent pregnancy is low.

Unilateral renal agenesis. Unilateral renal agenesis, defined as the complete absence of one kidney and its associated ureter, occurs in approximately 1 : 1000 to 1 : 1200 individuals. Males are affected nearly twice as often as females. The underlying cause is thought to be abnormal interaction between a ureteric bud and its associated metanephric mesenchyme; however, it is unclear why some patients develop unilateral agenesis, whereas in others both sides are affected.

Like bilateral agenesis, unilateral renal agenesis is often discovered using prenatal ultrasound, which reveals an empty renal fossa without evidence of ectopic renal parenchyma, such as a pelvic kidney. Unlike in bilateral agenesis, however, urine production is normal, and therefore oligohydramnios does not occur. As a result, affected infants are typically born with a normal appearance and normal pulmonary function.

Many patients with unilateral renal agenesis have associated abnormalities in other organ systems. Indeed, the absence of a kidney may not even be discovered until an associated abnormality is investigated. Many of these abnormalities occur in structures derived from the mesonephric or paramesonephric ducts, suggesting a defect in the intermediate mesoderm early in development. In males, the ipsilateral mesonephric duct derivatives (vas deferens, seminal gland [vesicle], and epididymis) may be absent or rudimentary (i.e., a seminal gland [vesicle] cyst). Meanwhile, in females, a common associated anomaly is a unicornuate uterus, in which the side ipsilateral to the absent kidney is missing.

Associated abnormalities may also occur in the cardiovascular system (e.g., septal or valvular defects) or gastrointestinal systems (e.g., imperforate anus).

ANOMALIES IN NUMBER OF KIDNEYS *(Continued)*

Nearby musculoskeletal abnormalities may also be seen. In a smaller subset of patients, unilateral renal agenesis may be associated with a genetic syndrome that affects numerous organ systems, such as BOR (branchio-oto-renal) syndrome, Turner syndrome, Fanconi anemia, Kallmann syndrome, VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal defects, limb defects), and others.

With a solitary kidney, renal function typically remains normal, although for unclear reasons there is an increased risk of vesicoureteral reflux, ureteropelvic junction obstruction, and ureterovesical junction obstruction. Later in life, some patients may develop renal insufficiency and proteinuria, likely secondary to hyperfiltration of the solitary kidney causing focal segmental glomerulosclerosis (see Plate 4-10). Their survival rate, however, appears to remain similar to that of normal individuals.

SUPERNUMERARY KIDNEY

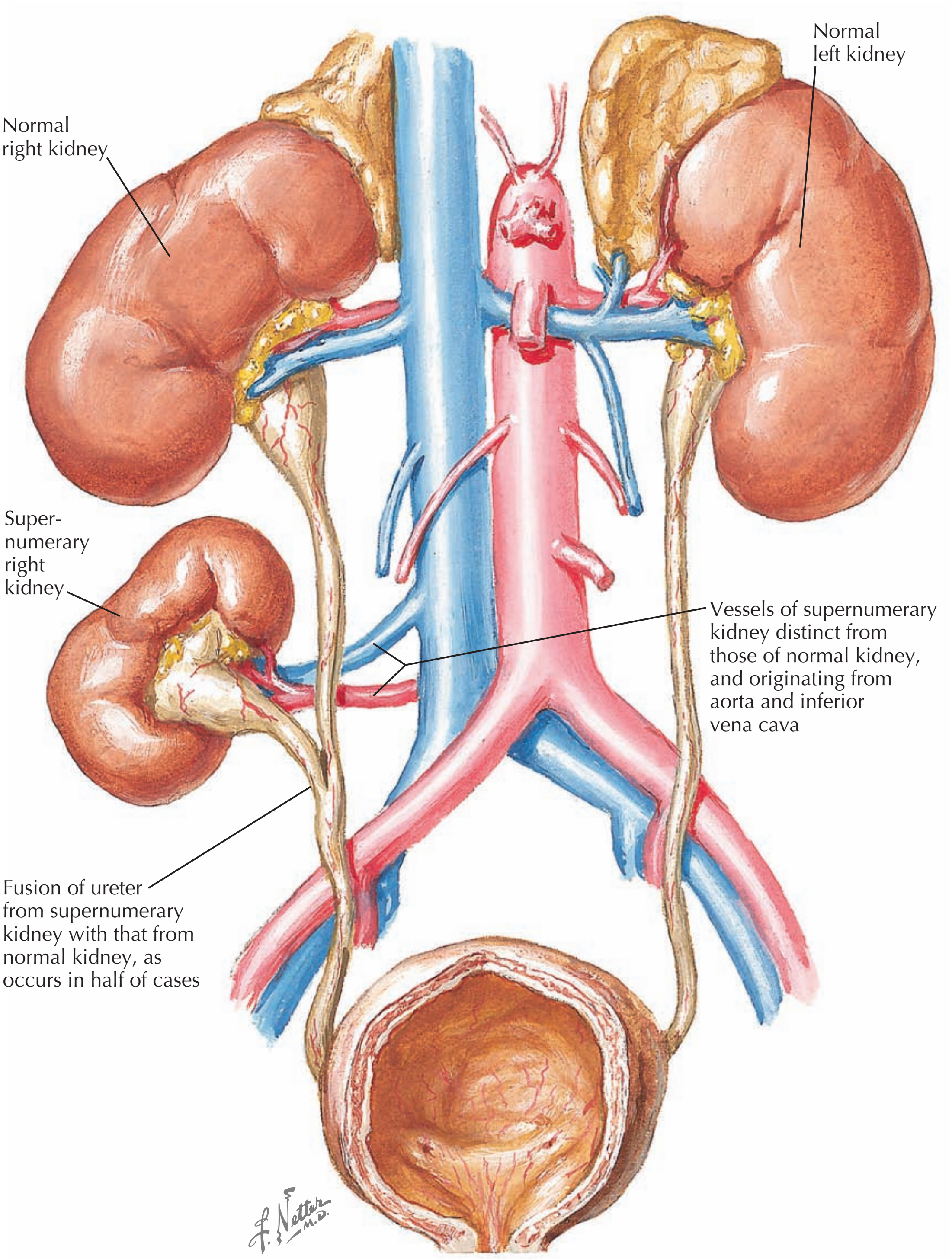
A supernumerary kidney is a very rare congenital anomaly. Unlike a kidney with a duplicated collecting system, which is far more common, a supernumerary kidney is a distinct mass of renal parenchyma with its own capsule, vessels, and collecting system. It is typically small and located just cephalad or caudal to the normally positioned kidney on the same side. Less commonly, it is located in a variety of other positions, such as the pelvis or midline. In some cases, the supernumerary kidney and normally positioned kidney may be loosely attached to each other by either fibrous tissue or a bridge of renal parenchyma.

In half of cases, the ureter associated with a supernumerary kidney fuses with that of the normally positioned ipsilateral kidney, as seen in the illustration; in the other half, the ureter has its own separate insertion into the bladder. In such cases, the Weigert-Meyer rule is usually obeyed, meaning that the ureter associated with the more caudally positioned kidney has an orifice located more superior and lateral than that of the cranially positioned kidney. The vessels to the supernumerary kidney usually originate from the aorta and inferior vena cava, although their origin is more variable with more caudally positioned kidneys.

The embryologic basis of the supernumerary kidney is not known but likely represents early division of the metanephric mesenchyme. A supernumerary kidney with a ureter that has its own insertion into the bladder likely reflects early division of the mesenchyme before insertion and branching of the ureteric bud (see Plate 2-2). The ureter to the supernumerary kidney probably represents a second ureteric bud that sprouted from the adjacent mesonephric duct, either by coincidence or as a direct effect of the divided mesenchyme. A supernumerary kidney with a ureter that fuses with that of the normal kidney likely reflects later division of the metanephric mesenchyme, perhaps in response to a ureteric bud that divided before insertion.

Supernumerary kidneys are often asymptomatic and do not affect overall renal function. Thus a significant number of such kidneys may never be discovered or may be noted only as incidental findings during the workup of another unrelated complaint. In some patients, however, supernumerary kidneys present as palpable abdominal masses or cause symptomatic nephrolithiasis or an upper urinary tract infection. Because of the rarity of this condition, affected patients are often not diagnosed until their fourth decade, if at all.

SUPERNUMERARY KIDNEY


Normal left kidney
Normal right kidney
Super-numerary right kidney
Vessels of supernumerary kidney distinct from those of normal kidney, and originating from aorta and inferior vena cava
Fusion of ureter from supernumerary kidney with that from normal kidney, as occurs in half of cases
F. Netter M.D.

RENAL FUSION

Development of the definitive adult kidney (metanephros) begins when the two ureteric buds invade the paired masses of metanephric mesenchyme (see Plate 2-2). Through a process known as branching morphogenesis, which depends on reciprocal signals between each ureteric bud and its associated mass of metanephric mesenchyme, the ureteric buds give rise to the ureters, renal pelves, calices, and collecting ducts, whereas the metanephric mesenchyme gives rise to nephrons.

Throughout this process, the two kidneys undergo separate but simultaneous development. As they undergo structural maturation, they also ascend in position (see Plate 2-5) from the sacral end of the fetus to the lumbar retroperitoneum.

Renal fusion can occur secondary to abnormalities in renal ascent, as in crossed renal ectopia (see Plate 2-6), or vice versa. In the former case, the superior pole of the crossed kidney ends up situated near the inferior pole of the normally positioned kidney, leading to fusion. In the latter case, a primary fusion event occurs, which then results in ectopia.

HORSESHOE KIDNEY

Horseshoe kidney, the most common type of renal fusion, occurs when an isthmus consisting of either fibrous tissue or functioning renal parenchyma connects the two kidneys in the midline. The overall incidence of this abnormality is estimated to about 1 : 600, with males affected twice as often as females. The horseshoe kidney is especially common in patients with chromosomal disorders, such as trisomy 18 and Turner syndrome.

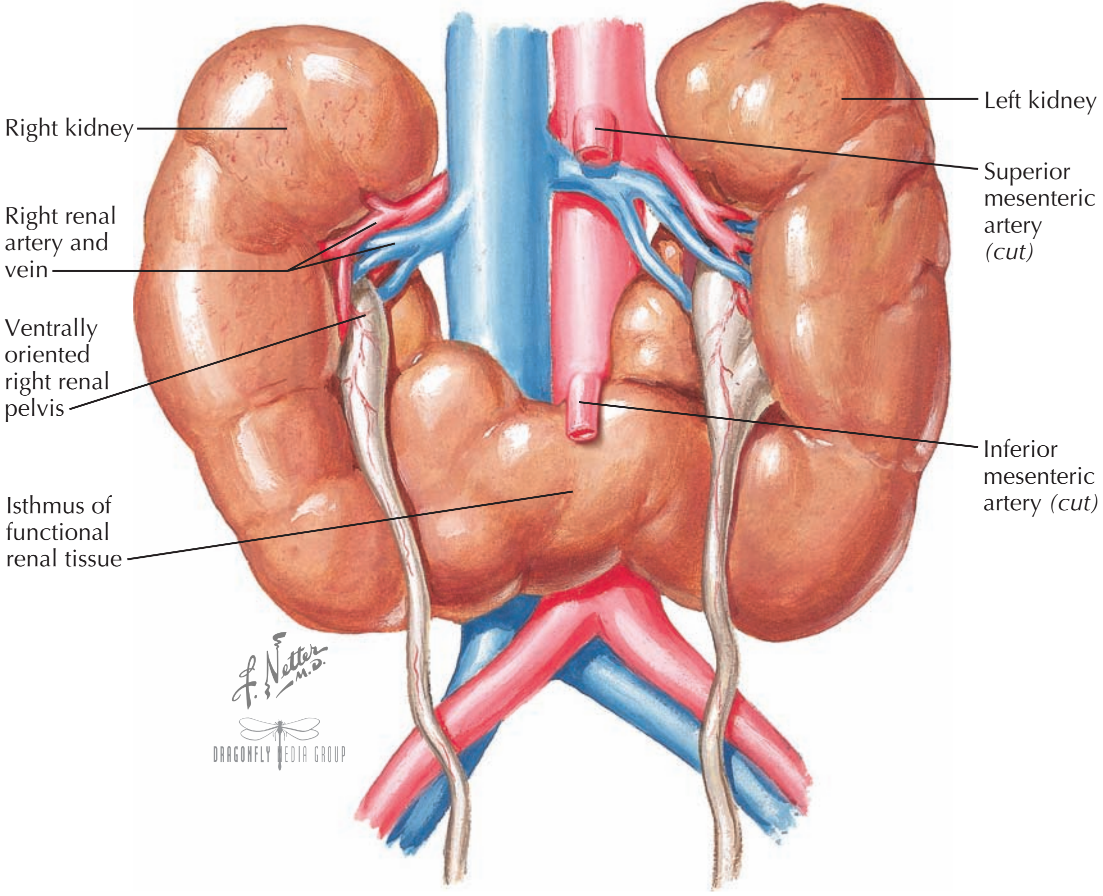
The horseshoe kidney is thought to result from fusion of the two metanephroi during the sixth week of development, while they are still near one another at the sacral end of the fetus. It is believed that abnormal lateral flexion of the embryo may dislocate one kidney more medially, approximating it near the contralateral kidney and causing a fusion event. Ascent of the fused horseshoe kidney is prematurely terminated when the isthmus reaches the level of the inferior mesenteric artery, beyond which it is unable to cross.

The horseshoe kidney is typically situated in the lower lumbar region, below the normal position of the mature kidneys. The isthmus almost always connects the lower poles of the two fused kidneys, although in rare cases it may join the upper poles instead. The isthmus is usually situated anterior to the aorta and the inferior vena cava but may rarely be situated between these vessels or posterior to them both. Both renal pelves are usually oriented ventrally or ventromedially, secondary to a failure of rotation. The ureters insert normally into the bladder but are prone to reflux. In about 10% of patients, ureteral duplication is seen (see Plate 2-23). The renal vasculature is variable. The upper poles of each kidney are usually perfused by one or more ipsilateral branches of the aorta, whereas the lower poles and isthmus may receive their own branches from the aorta, iliac, or sacral arteries.

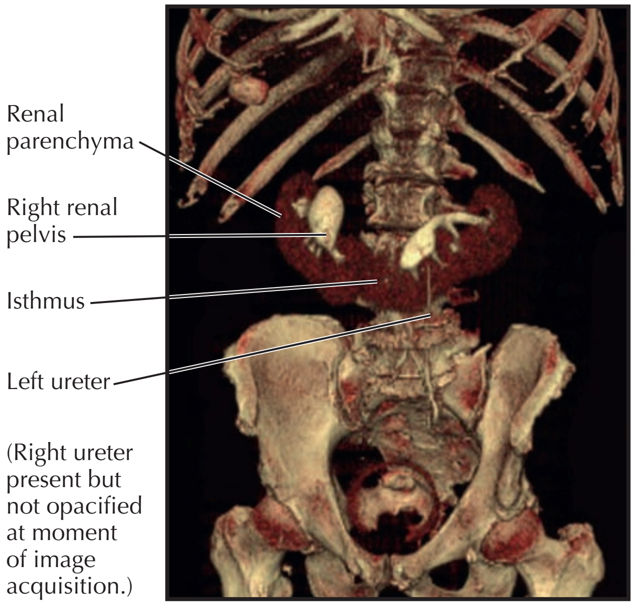
A horseshoe kidney rarely causes symptoms and is typically an incidental finding. A minority of patients, however, develop ureteropelvic junction obstructions, nephrolithiasis, or urinary tract infections. These complications may result from the abnormally high ureteropelvic junction or kinking of the ureters as they cross over the fused isthmus. In addition, some patients may experience traumatic injury to the isthmus due to its midline position anterior to the spine. A smaller subset of patients may present during childhood with Wilms tumor, as horseshoe kidney increases the risk.

A small subset of patients with horseshoe kidney have concomitant abnormalities in other organ systems. Associated genital abnormalities include hypospadias and undescended testes in males, or vaginal septation and bicornuate uterus in females. Other associated abnormalities include neural tube defects and cardiac ventriculoseptal defects.

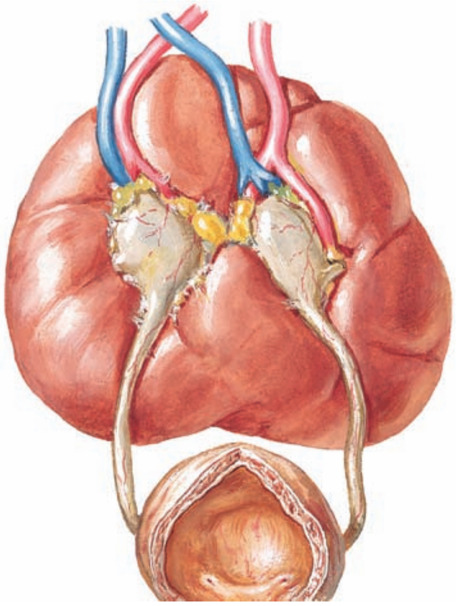
Horseshoe kidney: gross appearance


Right kidney
Right renal artery and vein
Ventrally oriented right renal pelvis
Isthmus of functional renal tissue
Left kidney
Superior mesenteric artery *(cut)*
Inferior mesenteric artery *(cut)*

Horseshoe kidney: radiographic findings (volume-rendered computed tomography)


Renal parenchyma
Right renal pelvis
Isthmus
Left ureter
(Right ureter present but not opacified at moment of image acquisition.)

Cake/lump kidney



LUMP/CAKE KIDNEY

The “lump” or “cake” kidney is a renal fusion variant in which there is complete merging of the two kidneys, such that two separate masses are no longer distinguishable. This anomaly reflects a very early, complete fusion of the metanephroi. The symptoms, risks, and treatment options are largely the same as for horseshoe kidney.

RENAL DYSPLASIA

Renal dysplasia refers to abnormal differentiation and organization of the renal parenchyma. The epidemiology is not known, since many patients with mild dysplasia are asymptomatic. Most cases appear to be sporadic.

A diagnosis of renal dysplasia can only be established based on histologic findings. Primitive-appearing ducts are generally seen surrounded by smooth muscle collars and embedded in a fibrous matrix. Primitive-appearing tubules are present and appear comma- or S-shaped, suggesting a developmental arrest during nephrogenesis. Glomeruli may be discernable but are poorly developed. Cystic dilation of glomeruli and ducts may also be seen. Finally, cartilaginous metaplasia is often but not invariably present. These dysplastic findings may be diffuse or focal.

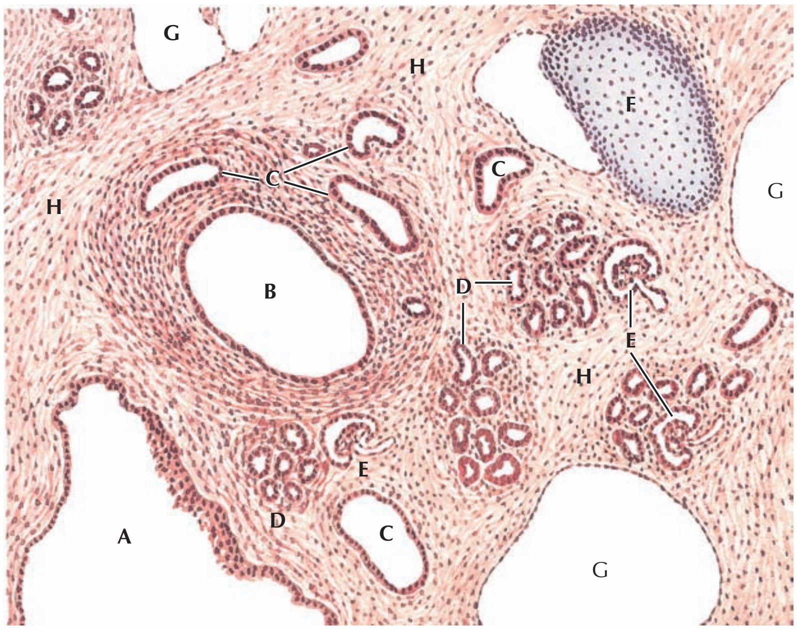
On gross examination, a dysplastic kidney may appear enlarged, hypoplastic or normal sized. If the contralateral unit is not dysplastic, it may nonetheless exhibit other abnormalities, such as hypoplasia, ectopia, ureteral stenosis, or ureterocele.

The causes of renal dysplasia are poorly understood and likely multifactorial. In some cases, it appears that early obstruction of the ureteric bud interferes with normal branching morphogenesis and induction of nephron formation. Such a mechanism would explain the association between renal dysplasia and conditions that cause congenital outflow obstruction, such as posterior urethral valves (see Plate 2-34) and bladder or cloacal exstrophy (see Plate 2-30).

Some patients, however, exhibit renal dysplasia in the absence of an outflow obstruction. In these cases, there are likely intrinsic defects in the signaling cascades that mediate the interaction between the ureteric bud and metanephric mesenchyme. The responsible abnormalities, however, remain poorly understood and are likely vast in number, given the wide range of different genetic syndromes that feature renal dysplasia as a component.

The clinical implications of renal dysplasia depend on its extent. Those with diffuse bilateral dysplasia produce little urine in utero, resulting in oligohydramnios and the Potter sequence (see Plate 2-8). In contrast, those with segmental unilateral disease may remain asymptomatic through adulthood.

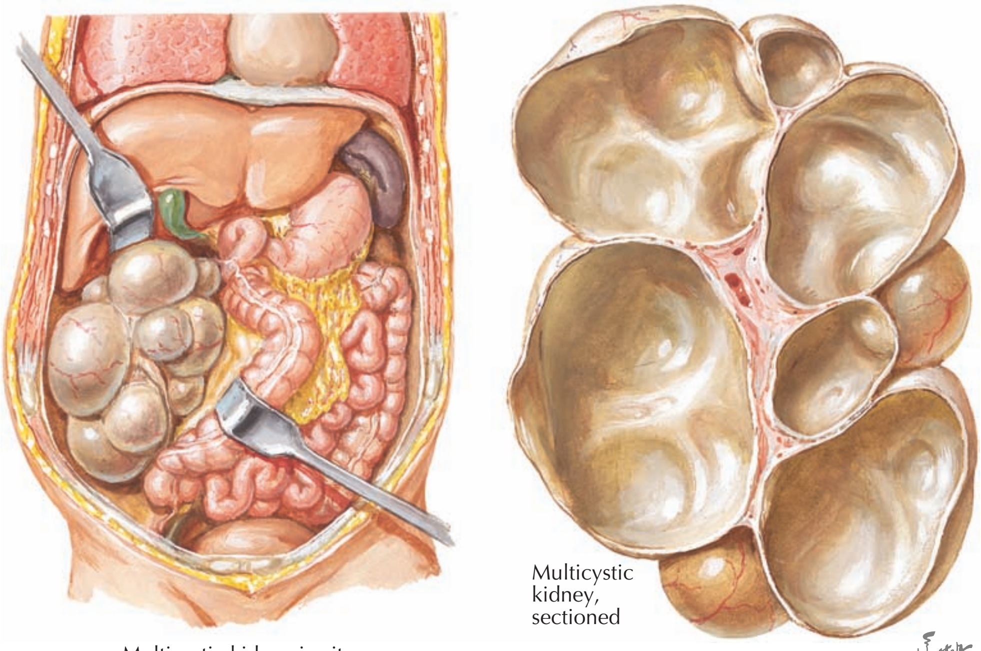
Light microscopy findings indicative of renal dysplasia



Findings in renal dysplasia, some or all of which may be present in varying degrees, either generalized or focally

A: Primitive pelvis
B: Primitive duct surrounded by fibromuscular collar
C: Primitive ducts
D: Primitive tubules
E: Primitive glomeruli
F: Cartilaginous metaplasia
G: Cysts
H: Interstitial fibrosis

Multicystic dysplastic kidney



Multicystic kidney in situ with narrow, cordlike ureter

Multicystic kidney, sectioned

F. Netter M.D.

MULTICYSTIC DYSPLASTIC KIDNEY DISEASE

Multicystic dysplastic kidney (MCDK) disease is an extreme form of cystic renal dysplasia. It is the most common cause of cystic kidney disease in children, with an estimated incidence of 1 : 3600 to 1 : 4300.

In most instances, nearly all renal tissue is replaced with cysts of varying sizes. Between the cysts are narrow septa consisting of dysplastic stroma and fibrous tissue. The kidneys may be small, normal, or enlarged, but they do not retain a normal reniform shape. A developed pelvicalyceal system is not present.

In about one fifth of cases, MCDK is bilateral, causing oligohydramnios and neonatal demise secondary to pulmonary hypoplasia. In the remaining cases, the contralateral kidney generally appears normal, but it is often subject to vesicoureteral reflux or ureteropelvic junction obstruction.

The pathogenesis of MCDK remains uncertain. As with renal dysplasia in general, congenital obstruction to urine outflow is thought to play a key role; however, early obstruction of the fetal ureter in animal experiments has so far failed to recreate the MCDK phenotype.

In most cases, the diagnosis of MCDK is first suspected through prenatal ultrasound. It may be difficult, however, to distinguish MCDK from congenital hydronephrosis, which is more common. In general, however, an MCDK features cysts of various sizes in a haphazard arrangement, whereas hydronephrotic kidneys contain a large central cystic region, representing the dilated renal pelvis, surrounded by smaller cystic regions, representing the dilated calices. In addition, the cysts of a MCDK generally do not appear continuous, unlike the dilated calices seen in hydronephrosis. If MCDK and hydronephrosis cannot be differentiated based on ultrasound, a postnatal renal scan may be helpful. An MCDK will show almost no radioisotope uptake, whereas a hydronephrotic kidney will exhibit some remaining function.

Once MCDK has been diagnosed, the contralateral kidney should be carefully assessed, and regular surveillance ultrasound should be performed to monitor the growth or degeneration of the MCDK.

In the past, MCDKs were often removed to prevent the development of Wilms tumor. Further research, however, has found that the risk of Wilms tumor in the MCDK is elevated but not enough to warrant routine removal (approximately 1 : 2000 compared with 1 : 8000 in a normal kidney). As a result, MCKDs are now removed only if their size interferes with the function of adjacent organs or surveillance ultrasound demonstrates changes concerning for neoplasm. In most cases, however, the MCKD undergoes spontaneous involution, and the long-term prognosis depends on the function of the contralateral kidney.

RENAL HYPOPLASIA

A normal kidney contains approximately 600,000 to 1,400,000 nephrons. Renal hypoplasia occurs when a kidney possesses such a significant reduction in its nephron endowment that it weighs less than half of the standardized mean. Renal hypoplasia can occur in association with otherwise normal renal development; in combination with renal dysplasia (i.e., hypodysplasia), in which case the renal parenchyma appears undifferentiated and disorganized; or as a secondary effect of conditions that cause renal atrophy or involution, such as chronic reflux nephropathy secondary to vesicoureteral reflux.

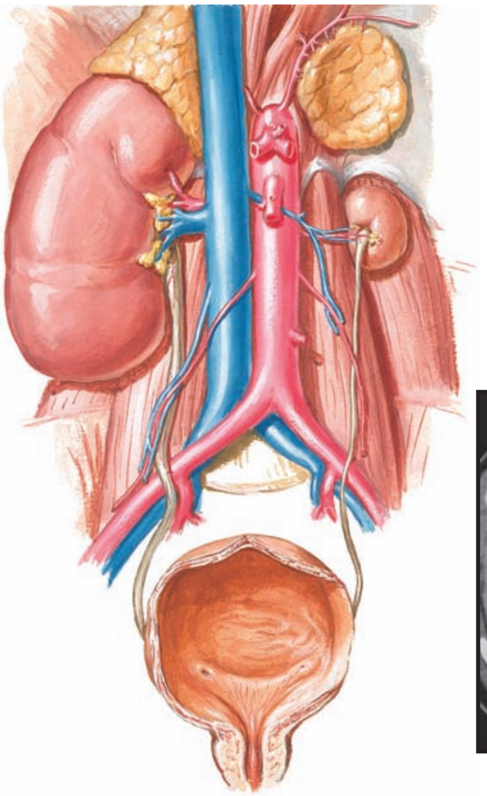
The incidence of hypoplasia without dysplasia is not known, but it is likely far rarer than hypodysplasia or atrophic renal hypoplasia. Two major forms of pure hypoplasia have been identified in the literature. The first, known as oligomeganephronia, is a mostly sporadic condition in which both kidneys possess a reduced number of nephrons, and the individual nephrons appear hypertrophic. The number of renal lobes is also reduced, with sometimes only one or two calices seen in each kidney. The second kind of hypoplasia, known as simple hypoplasia, is a much rarer, poorly described condition in which there is a reduced number of nephrons in one or both kidneys, but the individual nephrons do not appear hypertrophic.

PATHOGENESIS

Hypoplasia likely represents either a premature arrest of nephrogenesis or partial failure of the normal interactions between the metanephric mesenchyme and branching ureteric bud. In either case, genetic factors appear to play a significant role, and most of the current knowledge about the pathogenesis of renal hypoplasia comes from the study of genetic syndromes that feature it as a component. The renal coloboma syndrome, for example, features both optic nerve coloboma and renal hypoplasia, and it results from mutations in the *PAX2* gene, which encodes a protein that promotes branching and survival of the ureteric bud.

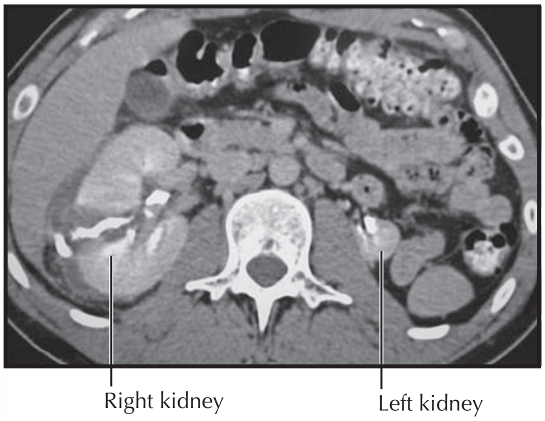
In addition to genetic factors, the intrauterine milieu and other environmental factors also appear to play a role. Both uteroplacental insufficiency and maternal malnutrition, for example, are known to cause intrauterine growth restriction and a reduced nephron endowment. Likewise, maternal vitamin A deficiency is associated with renal hypoplasia because it prevents normal production of the RET receptor, an essential component in normal nephrogenesis.

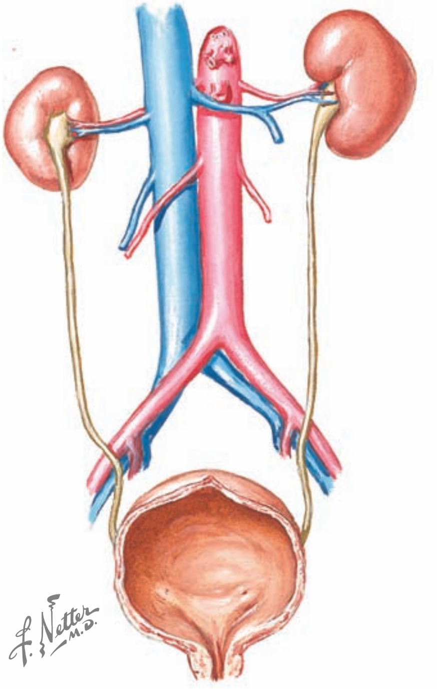
No matter the cause of hypoplasia, the small nephron population is often unable to provide a normal level of filtration function. Although the resulting renal insufficiency is initially offset by glomerular hyperfiltration, which increases the functional output of each nephron, this seemingly adaptive mechanism causes podocyte injury and can ultimately result in focal segmental glomerulosclerosis (FSGS, see Plate 4-10). As FSGS becomes more advanced, renal function continues to deteriorate, and end-stage renal disease (ESRD) eventually occurs.



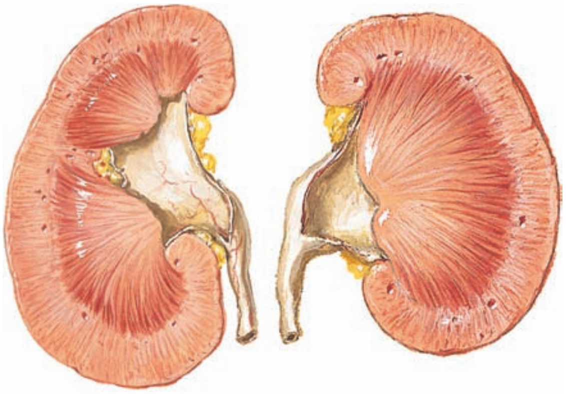
Gross appearance of shrunken left kidney secondary to hypoplasia or hypodysplasia. Note normally positioned left adrenal gland and normal-appearing right kidney.

Computed tomography (contrast enhanced) performed for blunt abdominal trauma reveals right-sided renal laceration and incidental finding of left-sided renal hypoplasia.





Gross appearance of oligomeganephronia, in which there is bilateral renal hypoplasia (with hypertrophy of individual nephrons seen microscopically).



Cut sections of kidneys in oligomeganephronia reveal simplified collecting systems with a reduced number of calices.

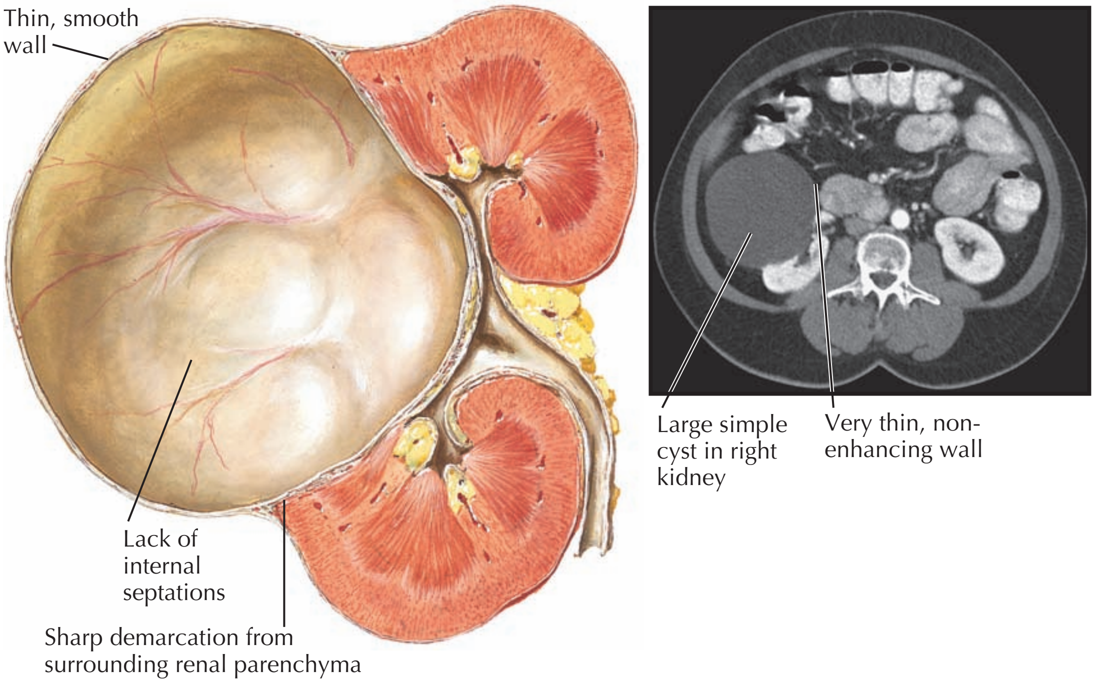
PRESENTATION AND DIAGNOSIS

Children with oligomeganephronia, the most common kind of pure renal hypoplasia, often present in the first years of life with evidence of renal insufficiency and dysfunction, including salt wasting, anorexia, vomiting, polyuria, polydipsia, and failure to thrive. Urine dipstick may reveal proteinuria if there is already a significant degree of FSGS, while serum chemistries reveal an elevated creatinine concentration. On ultrasound, the size of each kidney is less than two standard deviations below the mean size for patient age. Ultrasound alone, however, often cannot distinguish purely hypoplastic kidneys from those that are scarred and shrunken secondary to chronic reflux nephropathy. A renal scan may be useful in this setting, as purely hypoplastic kidneys generally lack focal areas of dysfunction, whereas kidneys with chronic reflux nephropathy exhibit areas of renal scarring that have reduced tracer uptake. Although a definitive diagnosis could be established with histopathologic examination of affected tissue, renal biopsy is rarely performed.

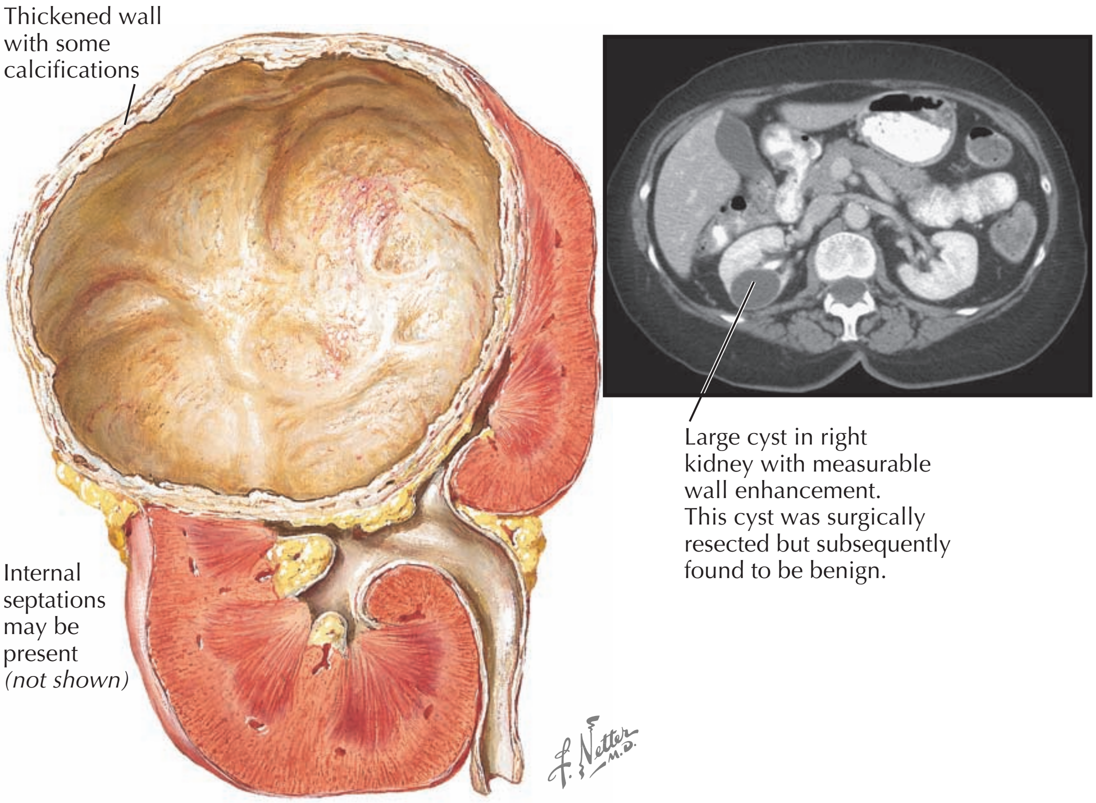
TREATMENT

The primary goal in the treatment of renal hypoplasia is to delay the onset of ESRD. As with any form of progressive renal insufficiency, controlling hypertension is essential because it reduces intraglomerular pressure and slows the progression of glomerulosclerosis. Angiotensin-converting enzyme (ACE) inhibitors are especially useful because they exert a selective vasodilatory effect on efferent arterioles, which further reduces intraglomerular pressure and also decreases proteinuria. Once ESRD occurs, however, renal transplantation becomes the only viable long-term solution.

Simple cyst (Bosniak class I)


Thin, smooth wall
Lack of internal septations
Sharp demarcation from surrounding renal parenchyma
Large simple cyst in right kidney
Very thin, non-enhancing wall

Complex cyst (Bosniak class III)


Thickened wall with some calcifications
Internal septations may be present *(not shown)*
Large cyst in right kidney with measurable wall enhancement.
This cyst was surgically resected but subsequently found to be benign.

SIMPLE CYSTS

Renal cysts sometimes occur as part of an inherited disease, such as polycystic kidney disease (see Plate 2-15), nephronophthisis/medullary cystic kidney disease (see Plate 2-18), tuberous sclerosis, or von Hippel-Lindau syndrome. In clinical practice, however, most renal cysts are sporadic and incidentally discovered during abdominal imaging performed for some other indication. Such cysts, known as "simple cysts," are very common among adults over the age of 50 and rarely cause symptoms.

Although a majority of renal cysts are benign and require no treatment, a subset may contain renal cell carcinoma and require surgical extirpation. In an attempt to quantify the likelihood of malignancy, each cyst is graded according to the Bosniak system, which considers its appearance and enhancement characteristics on computed tomography (CT).

A Bosniak I cyst is a true "simple cyst" and is the most common type of cyst seen in general practice. It is surrounded by a hairline thin, smooth, nonenhancing wall that sharply demarcates it from the surrounding renal parenchyma. No internal septations are seen. Its fluid contents appear homogeneous and nonenhancing, with the same density as water (–20 to 20 Hounsfield units [HU]). Calcifications and solid components are not seen. The risk of malignancy is near zero, and further evaluation is not required. Of note, a cyst seen on ultrasonography can also be classified as "simple" if it is anechoic, sharply defined, and has an enhancing posterior wall, which indicates adequate transmission through the fluid contents.

A Bosniak II cyst possesses a thin, smooth, nonenhancing wall but may also possess a few hairline septa with very fine or short areas of calcification. The septa may have "perceived contrast enhancement," meaning there is the subjective perception of slight enhancement, which has been ascribed to the presence of contrast in the fine capillaries that supply the septa. No enhancement, however, should be quantifiable. Also included in this category are nonenhancing cysts that are less than 3 cm in diameter and possess fluid contents with a uniformly higher attentuation than water because of the presence of degenerated blood. Like class I cysts, class II cysts have a very low risk of malignancy and often do not require further follow-up.

A Bosniak type IIF cyst may have minimal smooth thickening of its external wall, as well as a greater number of internal septa. In addition, thick or nodular areas of calcification may also be seen. Nonetheless, no actual contrast enhancement should be seen in the wall, septum, or fluid contents. Also included in this category are nonenhancing cysts greater than 3 cm in diameter that have uniformly hyperattenuating fluid contents. The "F" is for "follow" because these lesions should be closely followed with regular CT imaging, which will reveal whether they are stable or progressive.

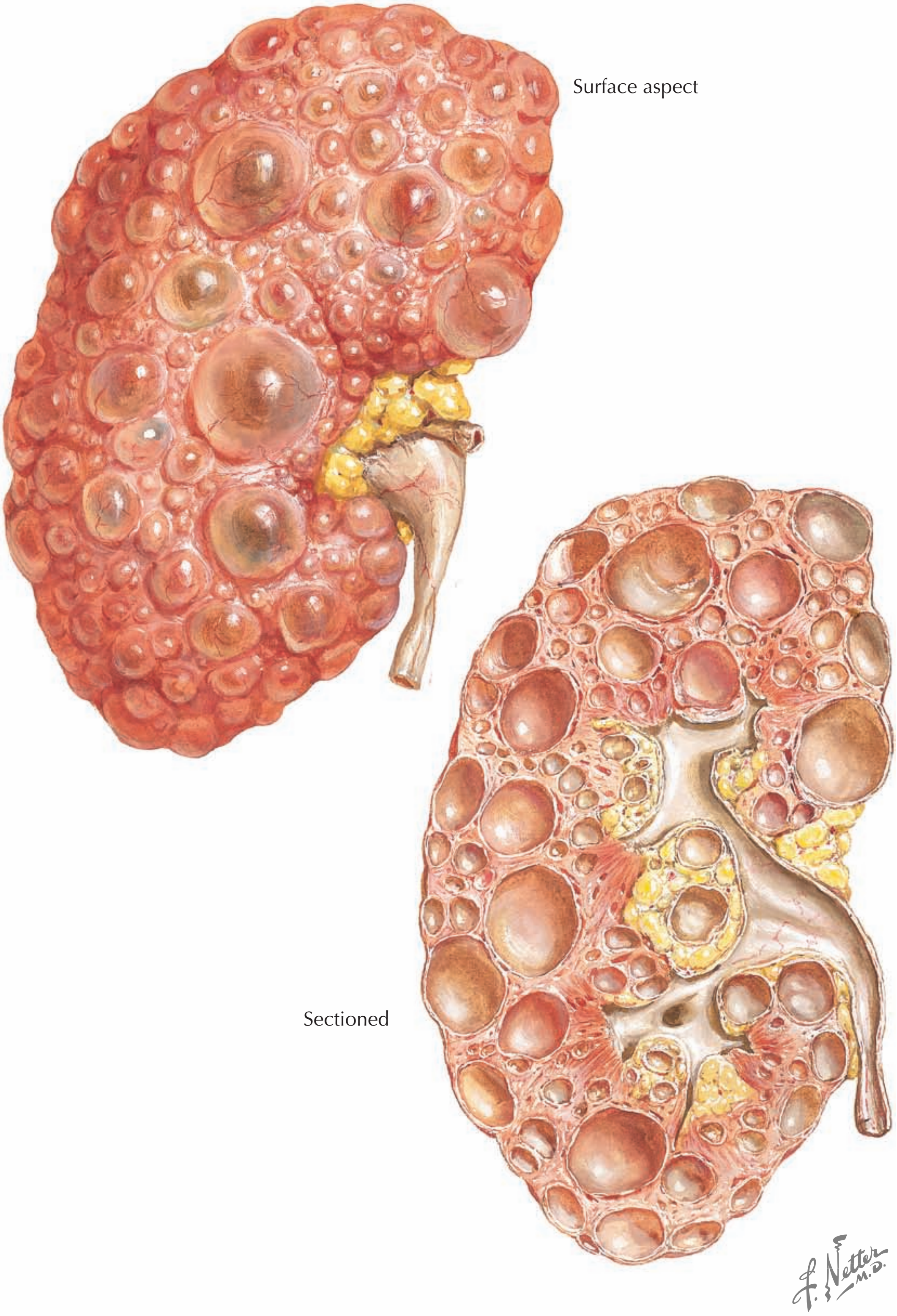
Bosniak III lesions have thickened, often calcified, smooth or irregular walls and septa that possess measureable enhancement (>15 HU). About half of these cysts are malignant, and thus surgical extirpation is generally indicated.

Bosniak IV lesions possess the characteristics of category III lesions and, in addition, have enhancing soft tissue components that are adjacent to but independent of the wall or septa. The vast majority of these cysts are malignant, and thus surgical resection is always indicated.

Polycystic Kidney Disease

Polycystic kidney disease is an inherited disorder that exists in both autosomal dominant and autosomal recessive forms (ADPKD and ARPKD, respectively). Both diseases are characterized by the bilateral, diffuse formation of renal cysts that replace normal parenchyma and cause progressive renal insufficiency.

Gross Appearance of Autosomal Dominant Polycystic Kidney Disease



ADPKD

ADPKD is a relatively common condition, with a prevalence of 1:400-1:1000, and it is responsible for approximately 5% to 10% of end-stage renal disease (ESRD). Most cases reflect autosomal dominant inheritance of the mutated gene from an affected parent, with complete penetrance; however, about 5% of patients have parents with normal kidneys, suggesting a *de novo* genetic mutation.

ADPKD is caused by mutations in the genes *PKD1* (chromosome 16p13.3) or *PKD2* (chromosome 4q21). *PKD1* mutations account for 85% of cases, whereas *PKD2* mutations account for the remainder. *PKD1* encodes polycystin-1, an integral membrane protein thought to play a role in cell-cell and cell-matrix interactions, while *PKD2* encodes polycystin-2, a cation channel involved in calcium signaling. Although polycystin-1 and polycystin-2 appear to interact with each other at primary cilia, the precise mechanism by which mutations in these proteins cause cyst formation remains unclear. It is generally accepted, however, that cystogenesis follows a two hit model. Although most renal tubules possess epithelial cells that contain one mutated allele and one normal allele, a small subset possess cells in which the normal allele also becomes mutated, which is the second “hit” that permits cyst formation.

There is a wide range of clinical phenotypes associated with ADPKD, ranging from a complete lack of symptoms to progression to ESRD. When symptomatic, the disease usually first presents in the third to fifth decade as flank pain and hematuria (reflecting either traumatic or atraumatic cyst rupture, nephrolithiasis, or infection), hypertension, and progressive renal insufficiency. Extrarenal disease manifestations are common, and they include hepatic cysts (in approximately 80%), pancreatic cysts (in approximately 10%), intracranial aneurysms (in approximately 10%), and mitral valve prolapse (in approximately 20%).

To some extent, the rate at which renal insufficiency progresses is dependent on the specific underlying mutation. Patients with *PKD1* mutations, for example, develop ESRD at a mean age of 54 years, whereas those with *PKD2* mutations develop ESRD at a mean age of 74 years. Even within the subgroup of patients with *PKD1* abnormalities, those with mutations near the 5′ end of the gene generally have a slightly faster progression to ESRD than those with mutations located near the 3′ end (53 years versus 56 years, respectively).

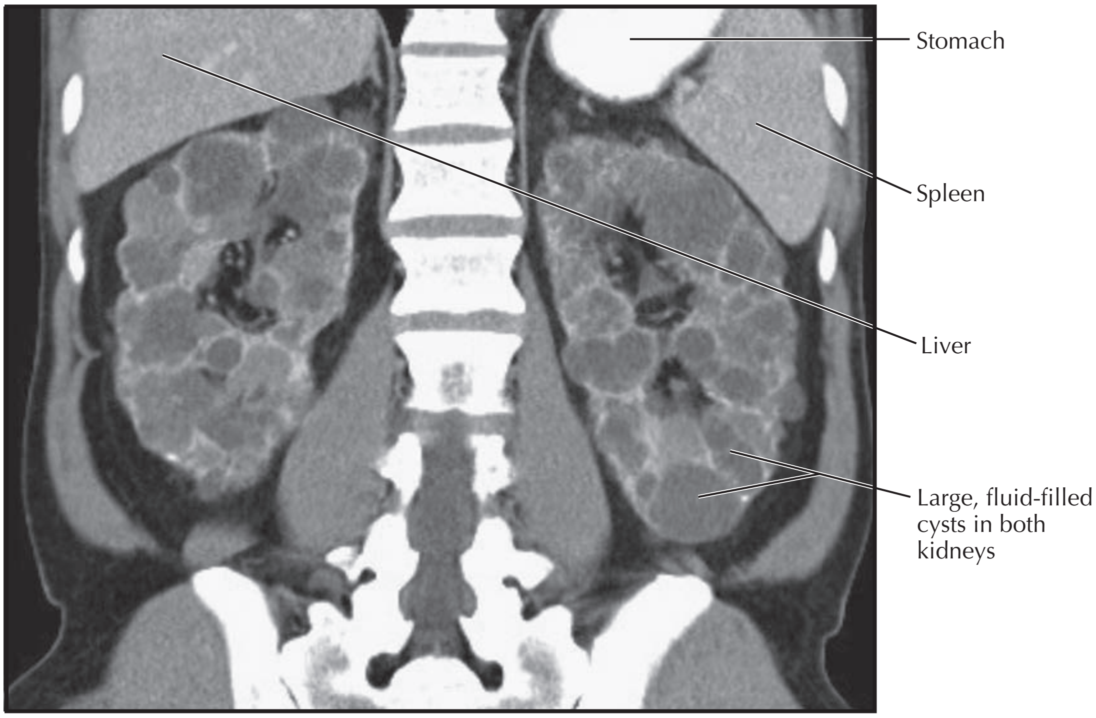
ADPKD can be diagnosed using several imaging modalities—such as ultrasound, CT, or magnetic resonance imaging—which reveal enlarged kidneys that possess diffuse, fluid-filled cysts. The cysts are variable in size, ranging from several millimeters to several centimeters, and are present in both cortex and medulla. The differential diagnosis should include other entities such as simple cysts (see Plate 2-14), especially when few cysts are seen; renal cyst formation secondary to other genetic syndromes, such as von Hippel-Lindau syndrome or tuberous sclerosis; medullary cystic kidney disease complex (see Plate 2-18); acquired cystic disease; and ARPKD, especially if cysts are noted early in life. The specific diagnosis of ADPKD can generally be reached based on the radiographic appearance of the kidneys, the presence of associated abnormalities (e.g., hepatic cysts), and a family history consistent with autosomal dominant transmission. Recent work has proposed the following sonographic criteria for the diagnosis of ADPKD in at-risk patients with families of unknown genotype: at least three unilateral or bilateral cysts in those 15 to 39 years of age; at least two cysts in each kidney in those 40 to 59 years of age; and four or more cysts in each kidney in those greater than 60 years of age. Due to the size and complexity of the *PKD1* and *PKD2* genes, genetic testing is not commonly performed.

At present, no directed treatment is available to prevent or slow further cyst formation, although several experimental therapies are being studied. Instead,

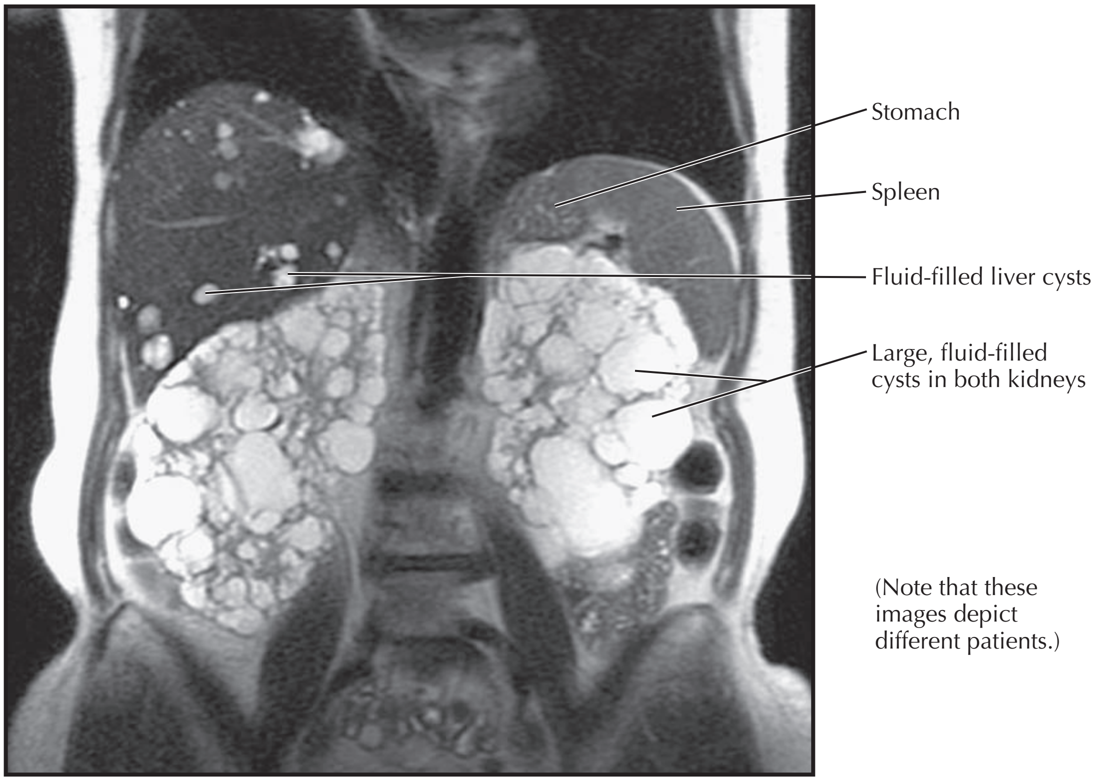
POLYCYSTIC KIDNEY DISEASE

(Continued)

RADIOGRAPHIC FINDINGS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE



Computed tomography (coronal reconstruction) with oral and intravenous contrast



(Note that these images depict different patients.)

Magnetic resonance imaging, T2-weighted sequence

treatment is chiefly directed at reducing the morbidity associated with complications of the renal cysts, such as pain, hemorrhage, infection, and hypertension. If pain becomes severe, some centers offer laparoscopic unroofing of cysts or percutaneous aspiration of cyst fluid and injection of sclerosing material. Hepatic cysts are usually asymptomatic, but in rare cases portal hypertension may occur. About 10% of those with ADPKD and intracranial aneurysms will die of subarachnoid hemorrhage; however, screening for intracranial aneurysms is generally not performed unless there is a family history of aneurysm rupture, the patient has a high-risk occupation (e.g., pilot), or there are concerning neurologic symptoms.

If progression to ESRD occurs, dialysis or renal transplantation is required. Before transplantation, nephrectomy may be necessary not only to relieve symptoms associated with the enlarged kidneys, but also to provide space for the graft.

ARPKD

ARPKD is a much rarer condition than ADPKD, occurring in approximately 1:20,000 live births. It is caused by mutations in the gene *PKHD1* (located on chromosome 6p21), which encodes a protein known as fibrocystin. Fibrocystin is localized to the primary cilia of epithelial cells in the thick ascending limb and collecting duct, as well as to epithelial cells lining the hepatic biliary ducts. Although fibrocystin appears to interact with polycystin-2, it is uncertain how abnormalities in this system result in cyst formation.

As with ADPKD, there is a wide range of clinical phenotypes, but patients present much earlier in life. All patients with ARPKD have congenital hepatic fibrosis, and some patients also have dilation of the intraductal biliary ducts (Caroli disease). In general, there is an inverse correlation between the severity of the renal disease, which typically presents during the neonatal period, and hepatic disease, which typically presents during late childhood or adolescence.

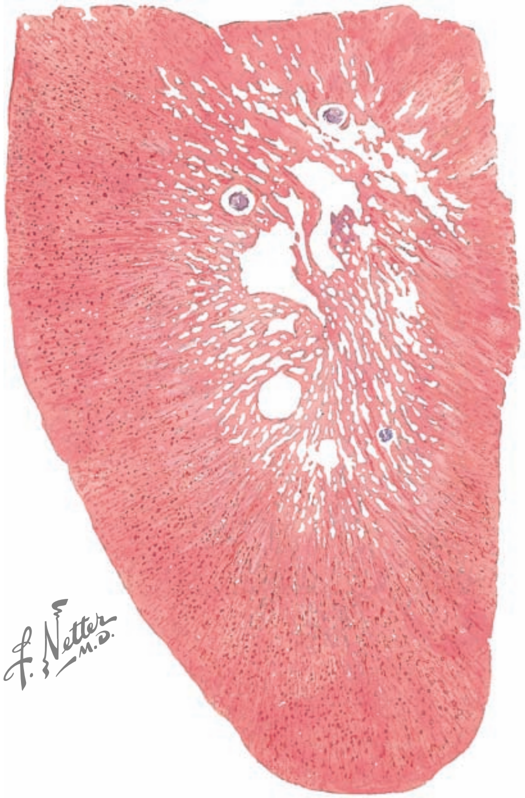
In patients with severe renal disease, the diagnosis is first apparent using prenatal ultrasound. The kidneys appear enlarged and hyperechogenic owing to the presence of innumerable cysts. Unlike in ADPKD and most other cystic diseases, however, the individual cysts are generally too small to be visualized. If renal dysfunction is severe enough, oligohydramnios may also be present. During delivery, the enlarged kidneys may cause dystocia. Shortly after birth, the neonate may experience respiratory distress if pulmonary hypoplasia has occurred secondary to oligohydramnios or if the kidneys are large enough to cause restrictive lung disease. Patients with milder renal disease may not present until childhood, when renal insufficiency manifests as electrolyte disturbances or hypertension. Unlike in ADPKD, hematuria and infection are not common features.

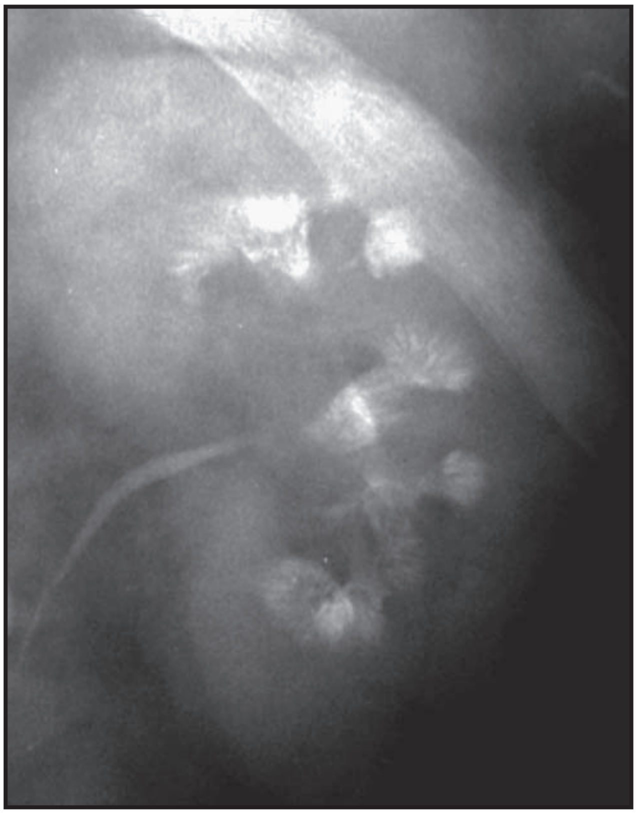
Patients with the mildest renal disease often present in late childhood or adolescence with symptoms referable to hepatic disease. In these patients, progressive hepatic fibrosis can result in portal hypertension, which can manifest as bleeding varices or splenic enlargement with cellular sequestration. Intrahepatic biliary duct dilation, if present, may also present as cholangitis.

The diagnosis of ARPKD is generally established based on the sonographic appearance of the kidneys, described previously, in association with evidence of hepatic fibrosis and a family history that demonstrates autosomal recessive transmission. If the diagnosis is in doubt, or if family members wish to establish their carrier status, genetic testing is available. Renal biopsy is seldom performed, but the major feature is the presence of elongated cortical and medullary cysts that arise predominantly from collecting ducts.

As with ADPKD, no directed treatment is available to prevent or slow cyst formation, and thus care should be directed toward managing complications of renal or hepatic dysfunction. Patients who present early in life with renal dysfunction require aggressive support to maintain adequate nutritional status and avoid sustained fluid or electrolyte abnormalities. Patients who have portal hypertension complications may require intervention, such as portosystemic shunting or variceal sclerotherapy. The timing of ESRD onset is variable, but when it occurs dialysis and renal transplantation become the only remaining therapeutic options.

MEDULLARY SPONGE KIDNEY


Section through lower pole of kidney, which reveals cystic dilation of the medullary collecting ducts. Some contain small calculi. The cortex appears normal.


Intravenous pyelogram (excretory phase) shows contrast collecting in the cystic medullary collecting ducts, which resemble brush-like striations radiating from the papillae.

Medullary sponge kidney (MSK) is a congenital disorder in which there is cystic dilation of the medullary collecting ducts. The dilated ducts generally have a diameter of 1 to 3 mm, although in some cases they may be as large as 5 to 7 mm. In most cases, both kidneys are involved, but in some cases the disorder is limited to one kidney or even to one or two pyramids.

PATHOGENESIS

MSK can occur either as an isolated phenomenon or in association with various genetic syndromes, such as congenital hemihypertrophy, Beckwith-Wiedemann syndrome, Marfan syndrome, and Ehlers-Danlos syndrome. It is generally considered to be sporadic, although there have been some reports of families with autosomal dominant inheritance. The pathogenesis of MSK is not known but is thought to involve abnormalities in the ureteric buds, which give rise to the ureters, renal pelves, calices, and collecting ducts during development of the metanephros (see Plate 2-2).

PRESENTATION AND DIAGNOSIS

MSK is generally a benign disorder that does not cause any symptoms. Therefore, for many patients, the abnormality is either never discovered or is only incidentally seen during radiographic evaluation of the abdomen for some other indication. In some cases, however, patients have nephrolithiasis, urinary tract infection, and/or hematuria, generally during adulthood.

The increased formation of nephrolithiasis in this disorder is thought to reflect numerous factors, including urine stasis in the dilated collecting ducts, as well as an increase in urine pH secondary to poor acidification in the dilated collecting ducts. Moreover, for uncertain reasons, patients are at increased risk of hypocitraturia and hypercalciuria, both of which promote calcium stone formation. The increased risk of urinary tract infection likely results from the presence of urinary stasis and stones. Finally, hematuria can occur with or without stones or infection, and it can be either gross or microscopic.

In many patients, the dilated collecting ducts also become dysfunctional. Impaired urine concentration may occur, for example, although it generally does not lead to polyuria. Likewise, incomplete distal renal tubular acidosis (see Plate 3-25) is common, but it does not generally lead to systemic acidosis.

The diagnosis of MSK is typically established with intravenous pyelography or contrast-enhanced CT. During the excretory phase, the dilated, contrast-filled medullary collecting ducts form striations that may be seen radiating from the calices in a brushlike pattern. Using CT, small calculi may also be seen in the dilated collecting ducts.

TREATMENT

There is no directed treatment for MSK. Patients who experience nephrolithiasis should increase their water intake and may benefit from treatment with thiazides and potassium citrate. When stones occur, they are generally small and undergo spontaneous passage; however, an intervention such as ureteroscopy (Plate 10-33) or extracorporeal lithotripsy (Plate 10-12) may sometimes be required.

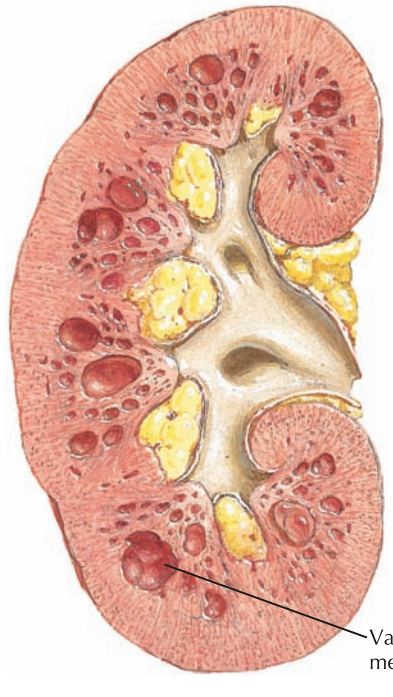
In general, the prognosis for patients with MSK is excellent. In rare cases, however, repeated episodes of nephrolithiasis or infection may lead to some degree of renal insufficiency.

NEPHRONOPHTHISIS/MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX

Nephronophthisis and medullary cystic kidney disease (MCKD) are both inherited diseases of the renal tubules. They share several clinical and pathologic features, including progressive renal insufficiency with a bland urine sediment, macroscopic cysts at the outer medulla and corticomedullary border, microscopic dilation and atrophy of the distal tubules and collecting ducts, lamellation and splitting of the tubular basement membranes, lymphocytic interstitial infiltrate, and interstitial fibrosis.

Because of their similarities, nephronophthisis and MCKD are generally considered to be components of a single disease complex. Despite this association, however, they differ in several important respects, including mode of inheritance, age at onset of end-stage renal disease (ESRD), and presence of extrarenal manifestations.

Renal abnormalities


Variable number of macroscopic cysts in medulla and at corticomedullary junction

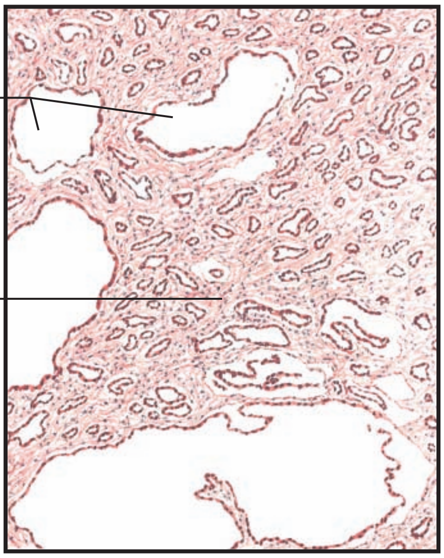
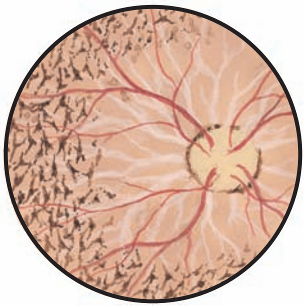

Dilated distal tubules and collecting ducts
Interstitial inflammatory cell infiltrate, with interstitial fibrosis

Illustration of light microscopy

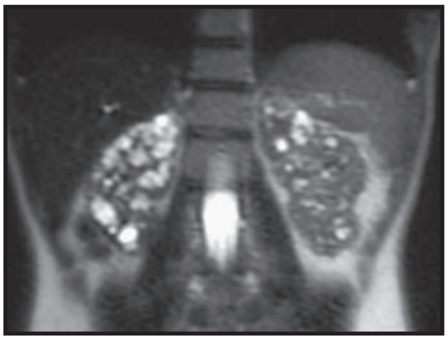
Extrarenal manifestations



Retinitis pigmentosa may occur in nephronophthisis, with the combination known as Senior-Løken syndrome

Gout common in type 2 medullary cystic kidney disease

Radiographic findings



T2-weighted magnetic resonance imaging reveals non-enlarged kidneys with numerous small cysts

NEPHRONOPHTHISIS

Nephronophthisis is an autosomal recessive disorder that accounts for approximately 5% to 10% of childhood ESRD in North America. Three different forms have been described—known as infantile, juvenile, and adolescent—that differ based on the age when ESRD occurs. The juvenile form is most common, with ESRD occurring at a mean age of 13 years. The adolescent form leads to ESRD at a mean age of 19 years, while the infantile form leads to ESRD at a mean age of 2 years.

Mutations in at least nine different genes, known as *NHPH1* through *NHPH9*, have been shown to cause nephronophthisis. Mutations in *NHPH1* account for about 20% of overall cases and result in juvenile nephronophthisis. This gene, located at chromosome 2q12.3, encodes nephrocystin-1, a protein involved in the adhesion of tubular epithelial cells both to each other and to the tubular basement membrane. The remaining *NHPH* genes each account for only about 3% of cases. Thus a significant number of cases result from mutations in as yet unidentified genes.

Affected patients usually first have polyuria and polydipsia, which reflect sodium wasting and defective urine concentration. On further evaluation, the clinical picture is consistent with nephrogenic diabetes insipidus. Over subsequent years, renal insufficiency supervenes, eventually progressing to ESRD. The urine sediment is typically benign. Extrarenal manifestations may be noted in some patients—including retinitis pigmentosa, hepatic fibrosis, skeletal defects, and cerebellar aplasia—depending on the underlying gene that is mutated.

If nephronophthisis is suspected, genetic testing can establish the diagnosis. Contrast-enhanced axial imaging may reveal the presence of macroscopic, predominantly medullary cysts in small- or normal-sized kidneys, in contrast to the enlarged kidneys seen in ADPKD. Renal biopsy, although not necessary for diagnosis, reveals the characteristic findings described above.

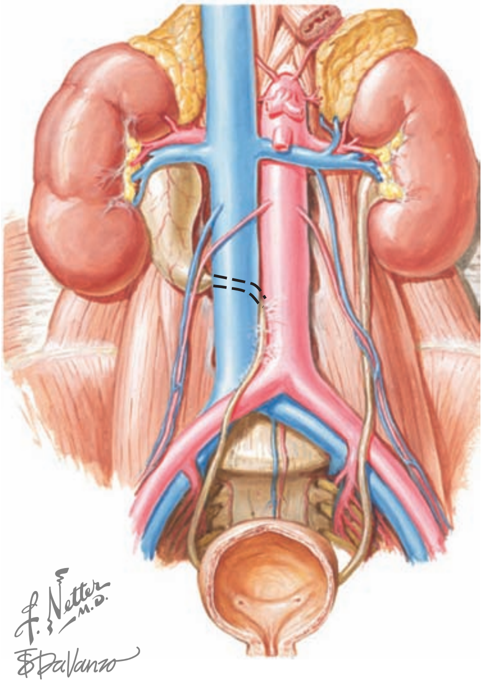
There is no directed therapy available for nephronophthisis, and affected patients invariably progress to ESRD. When possible, renal transplantation is appropriate.

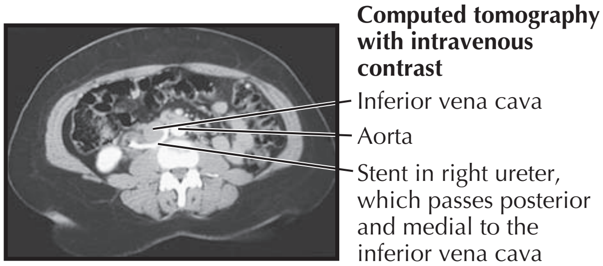
MEDULLARY CYSTIC KIDNEY DISEASE

MCKD is a rare autosomal dominant disorder that exists in two different forms. Type 1 results from mutations occurring at a locus on chromosome 1q21. The major clinical manifestation is renal insufficiency with a bland urine sediment, which appears during the third decade or later and is slowly progressive. Unlike in nephronophthisis, polyuria and polydipsia may not be prominent. Renal biopsy can suggest the diagnosis, which is then established with genetic testing. Treatment is supportive, and once ESRD occurs, renal transplantation is appropriate.

Type 2 MCKD (also known as familial juvenile hyperuricemic nephropathy) reflects mutations in the *UMOD* gene, located on chromosome 16p12. This gene encodes uromodulin, also known as Tamm-Horsfall mucoprotein, which is produced in the thick ascending limb (TAL). The mutations causing type 2 MCKD interfere with the export of uromodulin from the tubular epithelial cells into the tubular lumen. The accumulation of abnormal uromodulin results in cell death and tubular atrophy. An increase in proximal salt reabsorption is typically enough to offset the salt wasting that would otherwise result from TAL dysfunction. Patients develop progressive renal insufficiency, however, that typically becomes apparent during the second decade. For uncertain reasons, patients also develop hyperuricemia, generally before the onset of renal dysfunction, that leads to recurrent episodes of gout. The combination of renal insufficiency, gout, and a family history of both should raise suspicion of the diagnosis of type 2 MCKD, which is established with genetic testing. Although treatment is mostly supportive, patients benefit from allopurinol, which reduces the incidence of gout attacks and, in some studies, has been shown to slow the progression to ESRD.

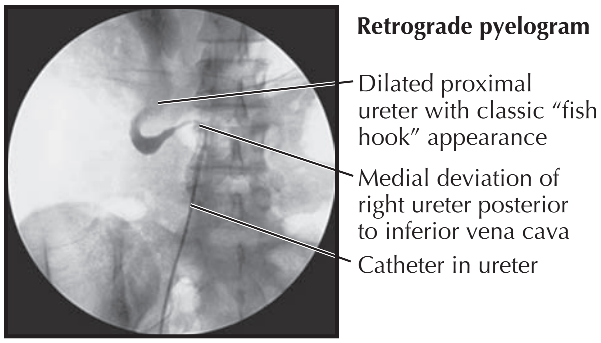
Radiographic Findings and Laparoscopic Repair of Retrocaval Ureter





Computed tomography with intravenous contrast

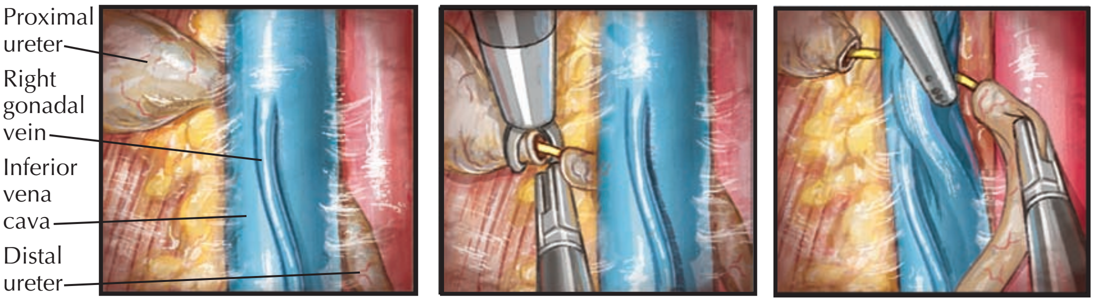
Inferior vena cava
Aorta
Stent in right ureter, which passes posterior and medial to the inferior vena cava



Retrograde pyelogram

Dilated proximal ureter with classic “fish hook” appearance
Medial deviation of right ureter posterior to inferior vena cava
Catheter in ureter

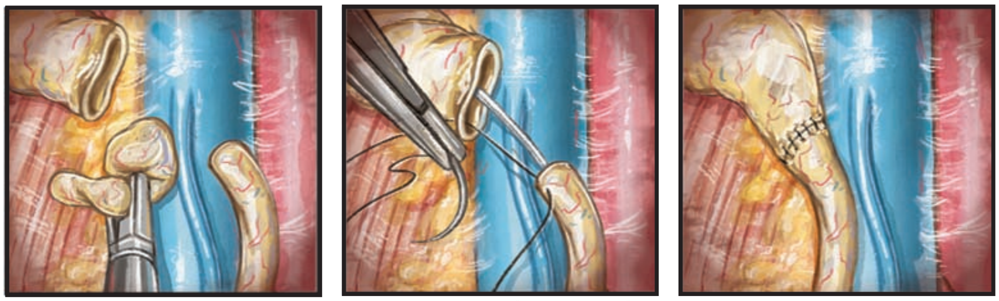
Laparoscopic repair of retrocaval ureter (ureteroureterostomy)



1. The ureter is visualized posterior to the inferior vena cava and dissected free.

2. The proximal ureter is divided, revealing a yellow stent placed endoscopically.

3. The distal ureter is pulled out from behind the inferior vena cava.



4. The proximal segment is incised to the level of the renal pelvis, which has a wide lumen that facilitates anastomosis.

5. A new stent, shown in white, is endoscopically placed into the distal segment under direct vision. End-to-end anastomosis of the two segments begins.

6. A watertight anastomosis is established, with the reconstructed ureter now lying lateral to the inferior vena cava.

RETROCAVAL URETER

The normal right ureter runs lateral to the inferior vena cava (IVC). A retrocaval (also known as circumcaval) ureter is a congenital anomaly in which the right ureter passes posterior to the IVC, emerges between the IVC and aorta, and then recrosses the iliac vessels anteriorly before inserting into the bladder. The portion of the ureter lying posterior to the IVC becomes obstructed, leading to dilation of the more proximal parts of the urine collecting system. This obstruction can become symptomatic during childhood or, more commonly, adulthood. The exact incidence of retrocaval ureter is uncertain but is likely 1 : 1000 to 1 : 1500, with males affected more often than females.

EMBRYOLOGY

A retrocaval ureter reflects abnormal development not of the ureter, but rather of the IVC. In the fourth week of gestation, the cardinal system of veins drains the body of the developing embryo. This system is divided into the two major branches: the anterior cardinal veins, which drain the superior portion of the embryo; and the posterior cardinal veins, which drain the inferior portion of the embryo. These join to form a common cardinal vein, which drains into the sinus venosus. Meanwhile, the vitelline veins, the precursors of the portal system, drain blood from the yolk sac to the sinus venosus. Finally, the umbilical veins carry oxygenated blood from the placenta to the embryo.

In the fifth week, the subcardinal veins develop parallel to the posterior cardinal veins. Both the subcardinal and posterior cardinal veins lie anterior to the developing ureters; however, as renal ascent progresses, the subcardinal veins become positioned medial to the ureters, whereas the posterior cardinal veins become lateral. During the fifth week, the sacrocardinal veins also appear at the caudal end of the posterior cardinal veins and lie posterior to the developing ureters.

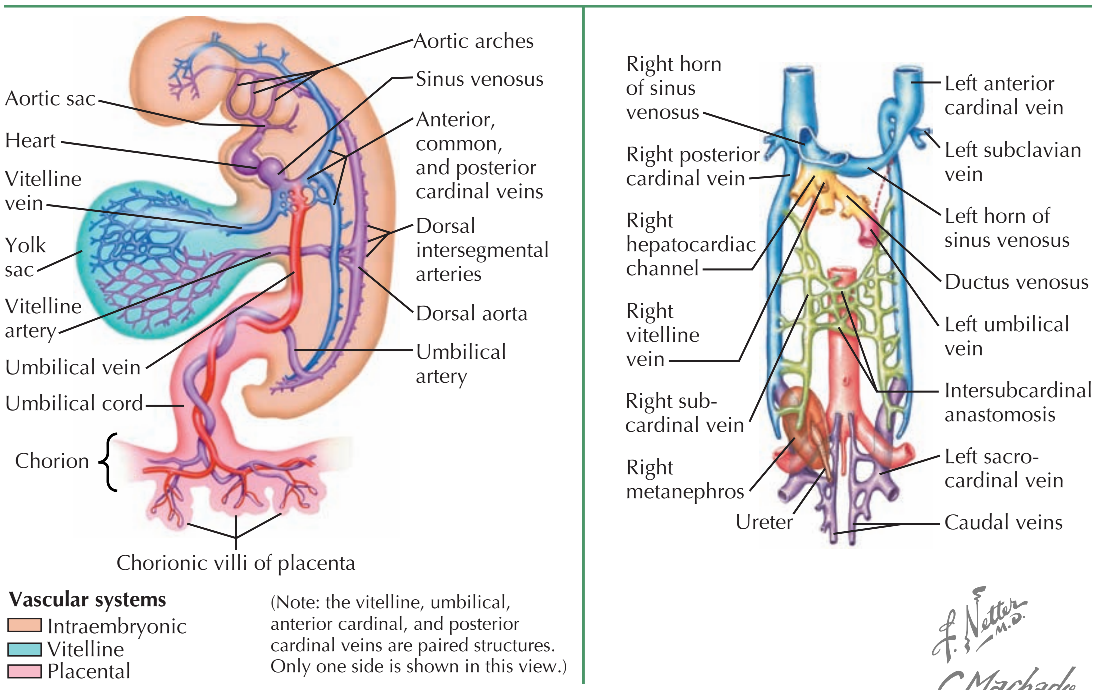
In the sixth week, the supracardinal veins form parallel to the posterior cardinal veins and largely take over their function of draining the posterior body wall. These lie medial to the posterior cardinal veins and dorsolateral to the developing ureters. As the supracardinal veins develop, the posterior cardinal veins degenerate. At this point, numerous anastomoses have formed between corresponding left- and right-sided structures.

During the sixth to eighth weeks of development, the IVC forms through the selective fusion and degeneration of these embryonic vessels. The sacrocardinal veins give rise to the common iliac veins and the distal end of the IVC. The right subcardinal vein gives rise to the renal segment of the IVC, as well as to the renal and gonadal veins. The right vitelline vein gives rise to the hepatic segment of the IVC. The supracardinal veins give rise to the azygous and hemiazygos veins. (According to some sources, the right supracardinal vein also contributes to the infrarenal segment of the IVC.)

As a result of this process, the entire IVC normally lies medial to the ureter. If, however, the right posterior

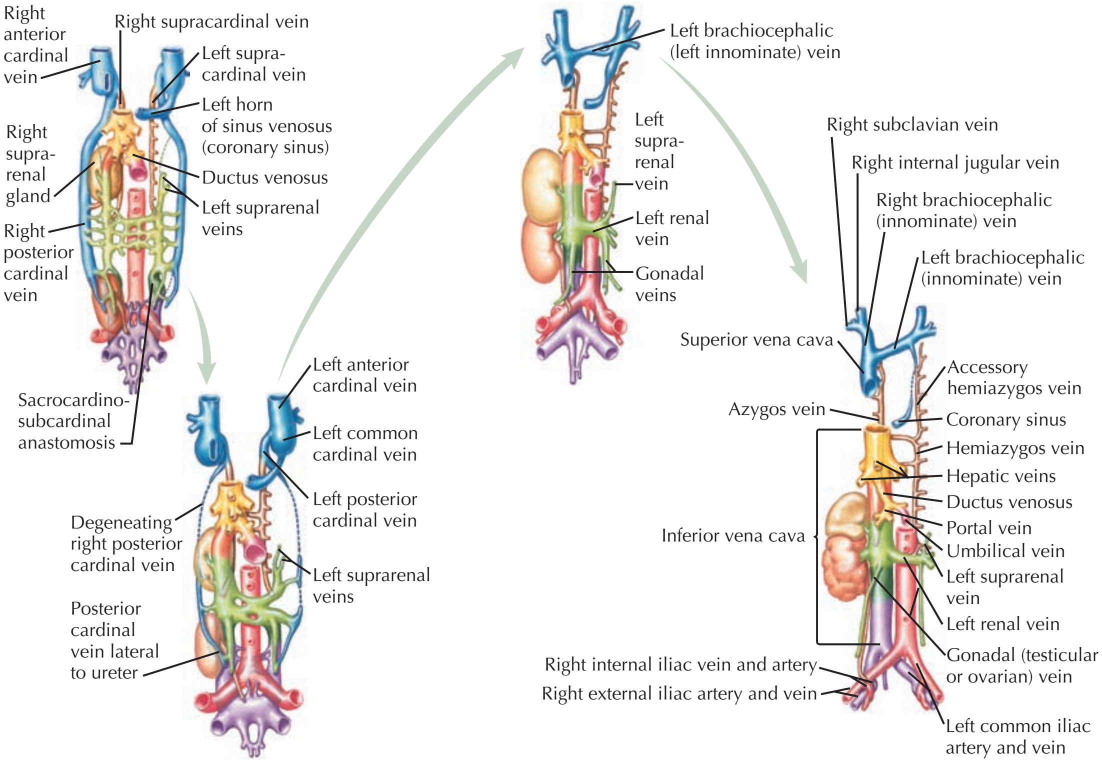
NORMAL DEVELOPMENT OF THE INFERIOR VENA CAVA

Vascular systems at fourth week (sagittal view) Venous systems at fifth week (frontal view)


Aortic arches
Sinus venosus
Aortic sac
Heart
Anterior, common, and posterior cardinal veins
Vitelline vein
Yolk sac
Dorsal intersegmental arteries
Vitelline artery
Dorsal aorta
Umbilical vein
Umbilical artery
Umbilical cord
Chorion
Chorionic villi of placenta
Vascular systems
🟧 Intraembryonic
🟦 Vitelline
🟥 Placental
Right horn of sinus venosus
Left anterior cardinal vein
Right posterior cardinal vein
Left subclavian vein
Right hepatocardiac channel
Left horn of sinus venosus
Ductus venosus
Right vitelline vein
Left umbilical vein
Intersubcardinal anastomosis
Right sub-cardinal vein
Left sacro-cardinal vein
Right metanephros
Ureter
Caudal veins
F. Netter M.D.
C. Machado M.D.

(Note: the vitelline, umbilical, anterior cardinal, and posterior cardinal veins are paired structures. Only one side is shown in this view.)

Formation of inferior vena cava from sixth to eighth weeks (frontal view)


Right anterior cardinal vein
Right supracardinal vein
Left supra-cardinal vein
Left horn of sinus venosus (coronary sinus)
Right supra-renal gland
Ductus venosus
Left suprarenal veins
Right posterior cardinal vein
Sacrocardino-subcardinal anastomosis
Left anterior cardinal vein
Left common cardinal vein
Degeneating right posterior cardinal vein
Left posterior cardinal vein
Left suprarenal veins
Posterior cardinal vein lateral to ureter
Left brachiocephalic (left innominate) vein
Left supra-renal vein
Left renal vein
Gonadal veins
Right subclavian vein
Right internal jugular vein
Right brachiocephalic (innominate) vein
Left brachiocephalic (innominate) vein
Superior vena cava
Accessory hemiazygos vein
Azygos vein
Coronary sinus
Hemiazygos vein
Hepatic veins
Ductus venosus
Portal vein
Inferior vena cava
Umbilical vein
Left suprarenal vein
Left renal vein
Gonadal (testicular or ovarian) vein
Right internal iliac vein and artery
Right external iliac artery and vein
Left common iliac artery and vein

RETROCAVAL URETER *(Continued)*

cardinal vein persists to form the renal segment of the IVC, then the ureter will lie medial and posterior to the IVC in the renal segment, causing it to take a retrocaval course.

PRESENTATION AND DIAGNOSIS

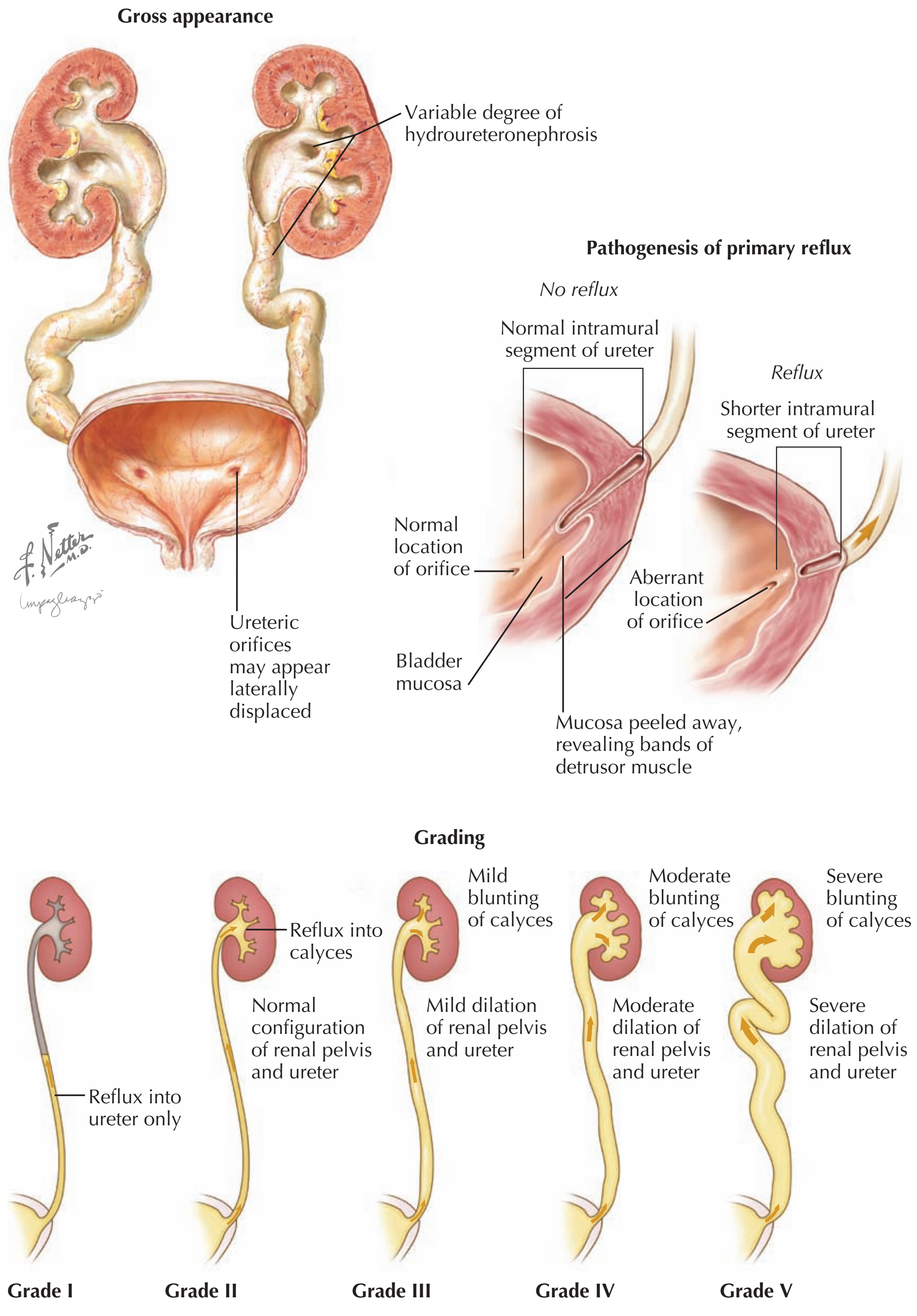
As expected, individuals with a retrocaval ureter have symptoms of ureteral obstruction, which include abdominal or right flank pain, chronic nausea, recurrent urinary infection due to urinary stasis, and hematuria following mild trauma. In many cases, however, symptoms either do not occur, or perhaps are not recognizable, until adulthood. The intermittent nature of renal colic often confuses the diagnosis. Moreover, the association with nausea often suggests gastrointestinal origin and delays diagnosis. Contextual clues of the pain facilitate the diagnosis. For example, pain may be more pronounced after ingestion of caffeinated or alcoholic beverages, which lead to brisk diuresis. Most often, the need for intervention becomes apparent when there is persistent right flank pain, stone formation, recurrent urinary tract infection, pyelonephritis, or deterioration of renal function.

If the clinical suspicion of retrocaval ureter is high, the diagnosis is confirmed using radiographic imaging. In the past, the standard evaluation began with intravenous pyelography, which reveals a variable degree of right-sided hydronephrosis, a medially deviated proximal ureter, a fish-hook or sickle-shaped appearance of the ureter just proximal to the IVC, and incomplete opacification of the ureter distal to the IVC. In the modern setting, contrast-enhanced CT is preferred. The size and contour of the entire ureter can be visualized in three dimensions with reconstruction of the axial images taken at the delayed urographic phase. Although a retrograde pyelogram can also be performed to visualize a retrocaval ureter, it is more invasive and also less detailed than CT.

TREATMENT

If intervention is needed, the ureter can be reconstructed by performing an open or laparoscopic ureteroureterostomy. Regardless of the modality, the basic steps of the procedure are the same. The renal pelvis and proximal ureter are dissected to the point where the ureter passes behind the IVC. The ureter is then divided adjacent to the lateral IVC wall, and the distal end of the ureter is removed from behind the IVC. (Some surgeons divide the ureter both lateral and medial to the IVC, effectively excluding the segment located behind the IVC.) The ureteral ends are repositioned such that the ureter takes a course lateral to the IVC. The proximal end of the ureter is typically long enough to make a tension-free, spatulated, end-to-end anastomosis without difficulty, which restores continuity to the ureter. A ureteral stent is deployed and left in position for several weeks after the procedure to ensure proper healing of the anastomosis.

MECHANISM AND GRADING OF VESICOURETERAL REFLUX


Gross appearance
Variable degree of hydroureteronephrosis
Ureteric orifices may appear laterally displaced
Pathogenesis of primary reflux
No reflux
Normal intramural segment of ureter
Normal location of orifice
Bladder mucosa
Mucosa peeled away, revealing bands of detrusor muscle
Reflux
Shorter intramural segment of ureter
Aberrant location of orifice
Grading
Reflux into ureter only
Reflux into calyces
Normal configuration of renal pelvis and ureter
Mild blunting of calyces
Mild dilation of renal pelvis and ureter
Moderate blunting of calyces
Moderate dilation of renal pelvis and ureter
Severe blunting of calyces
Severe dilation of renal pelvis and ureter
Grade I
Grade II
Grade III
Grade IV
Grade V

VESICOURETERAL REFLUX

Vesicoureteral reflux (VUR) is defined as the retrograde flow of urine from the bladder into the ureter and, in many cases, the renal pelvicalyceal system. This condition is considered problematic because it facilitates propulsion of bacteria toward the kidneys, which can cause recurrent pyelonephritis, renal scarring, and eventual renal dysfunction.

VUR is generally diagnosed during childhood. The overall incidence has been difficult to estimate because the condition is often undetected and frequently resolves with age. It has been reported, however, that 70% of infants who have urinary tract infections (UTIs) also have reflux. Although VUR is more common in male infants, it is more common in females after the first year of life.

PATHOGENESIS

Normal ureteral continence relies on a valve mechanism formed as the ureter courses between the bladder mucosa and detrusor muscle before terminating at the ureteric orifice. When the bladder contracts, compression of the intramural segment of each ureter prevents the retrograde flow of urine.

Primary reflux occurs when the ureterovesical junction (UVJ) is abnormal. In nonrefluxing UVJs, the length of the ureter's intramural segment is at least five times the ureteral diameter. In refluxing UVJs, in contrast, the intramural segment is too short or, less often, the ureteral diameter is too wide. As a result, the valve mechanism is inadequate to prevent the reflux of urine during bladder contraction. Although there is a clear genetic basis for VUR, as evidenced by high rates of concordance among monozygotic twins, the genes that modulate UVJ structure have not been identified.

Secondary reflux occurs when there are very high filling pressures in the bladder, which overwhelm otherwise normal ureterovesical junctions. In male infants, a common cause is posterior urethral valves (see Plate 2-34), which cause congenital bladder outlet obstruction. Other causes include neurogenic bladder, dysfunctional voiding, and ureterocele (see Plate 2-26).

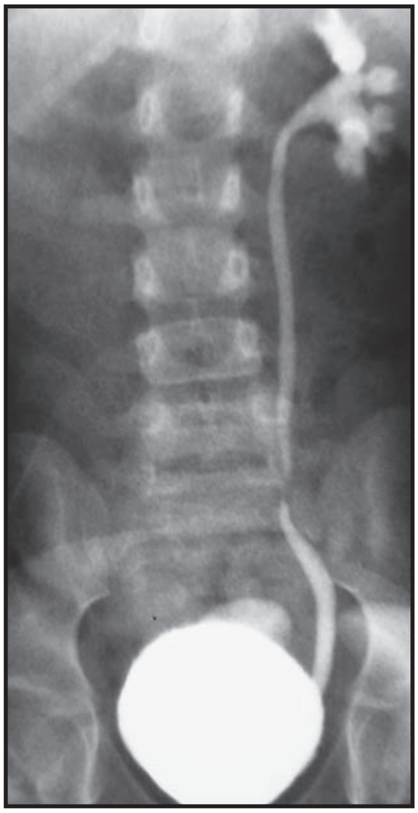
Although VUR is not itself a risk factor for lower urinary tract infection, it does permit the passage of bacteria from the bladder to the kidneys. Over time, repeated episodes of pyelonephritis can result in renal scarring and dysfunction, especially if infections occur in the first year of life. In contrast, the reflux of sterile urine does not appear to cause renal scarring at any age.

Of note, VUR also appears to be associated with a variable degree of renal dysplasia that is unrelated to infection. Indeed, both VUR and renal dysplasia could be expected to result from an abnormally caudal position of the ureteric bud on the mesonephric duct (see Plate 2-1) because this arrangement would cause both (1) suboptimal interaction between the ureteric bud and metanephric mesenchyme, as well as (2) a short intramural course for the ureter.

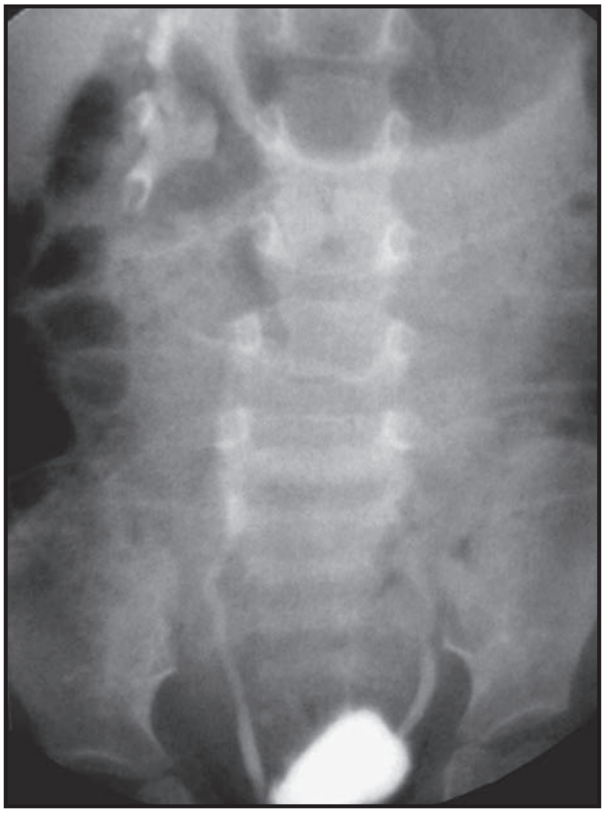
PRESENTATION AND DIAGNOSIS

VUR is generally first suspected when prenatal ultrasound reveals hydronephrosis or when a child develops

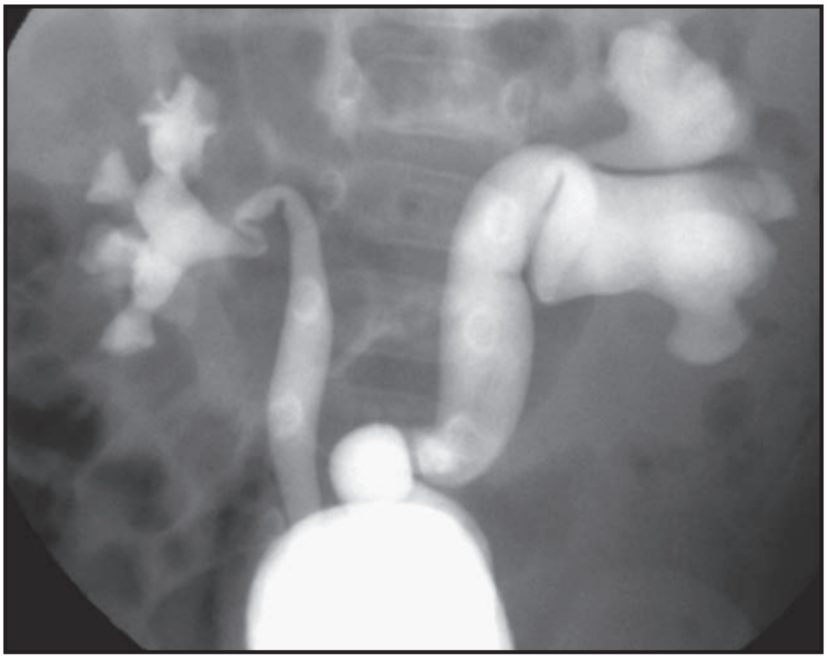
VOIDING CYSTOURETHROGRAMS DEMONSTRATING VESICOURETERAL REFLUX



Left-sided grade III reflux, no right-sided reflux



Left-sided grade I reflux, right-sided grade II reflux



Left-sided grade V reflux, right-sided grade IV reflux

VESICOURETERAL REFLUX
(Continued)

a UTI. Among infants, further workup is indicated if a repeat postnatal ultrasound reveals persistent hydronephrosis. Among children, further workup is indicated if a male child has a UTI, a female child less than 5 years of age has a UTI, or a female child of any age has a febrile UTI.

The gold standard diagnostic test is a voiding cystourethrogram (VCUG). In a VCUG, the bladder is instilled with contrast and examined under fluoroscopy while the patient voids. The diagnosis of VUR is established if contrast is seen entering one or both ureters. The severity of the reflux can be classified into one of five grades based on the International Reflux Grading system, as shown in the illustration on the opposite page.

TREATMENT

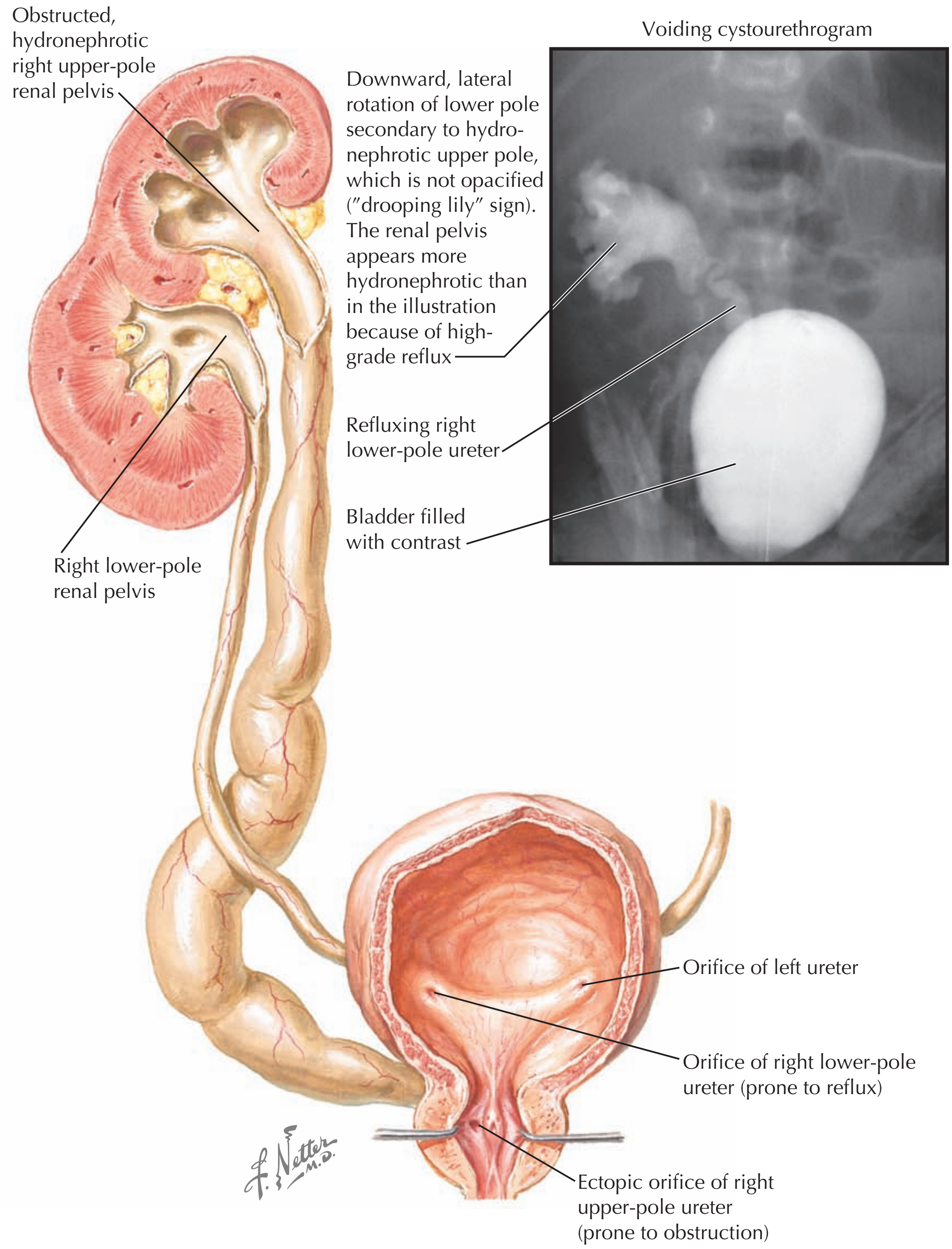
Patients with bilateral high grade VUR, particularly those with renal scarring, should undergo regular evaluation with measurement of height, weight, blood pressure, and serum creatinine concentration. Correction of any bladder or bowel dysfunction is critical, as it lowers the rate of UTIs and improves the probability that VUR will spontaneously resolve. Urinalysis should be performed on a regular basis, along with follow-up urine culture if there is evidence of bacteriuria or pyuria. Finally, ultrasound or renal scan may be performed to assess for the presence and degree of renal scarring.

The available treatment options for VUR depend on grade and laterality. They include observation with or without antibiotic prophylaxis, endoscopic bulking of the ureteric orifice, and ureteral reimplantation (see Plate 10-35). The relative risks and benefits of these different options remain uncertain, and as a result there is a wide variation in management strategies.

A majority of the children with low-grade primary reflux (grades I-III) experience spontaneous resolution, presumably because growth of the bladder leads to lengthening of the intramural ureteral segment. Thus most authorities recommend careful observation of such children and continuous antibiotic prophylaxis until the reflux resolves. Common agents include low dose trimethoprim-sulfamethoxazole or nitrofurantoin. Patients who have persistent reflux at 6 years of age that is either bilateral or associated with renal scarring may be candidates for surgical intervention. The first-line therapy should be endoscopic injection of bulking agents adjacent to the refluxing ureteric orifice, a minimally invasive procedure with high success rates in this group.

A majority of the children with high-grade primary reflux (grades IV and V) will not experience spontaneous resolution, and thus surgical treatment may be offered to lower the risk of renal scarring. Endoscopic techniques often fail to correct high-grade reflux, and thus open or laparoscopic reconstruction of the ureterovesical junction is typically performed. The cross trigonal ureteral implant is a popular technique (see Plate 10-35). Until the reflux is corrected, antibiotic prophylaxis should be provided to maintain sterile urine.

COMPLETE URETERAL DUPLICATION


Obstructed, hydronephrotic right upper-pole renal pelvis
Voiding cystourethrogram
Downward, lateral rotation of lower pole secondary to hydronephrotic upper pole, which is not opacified ("drooping lily" sign). The renal pelvis appears more hydronephrotic than in the illustration because of high-grade reflux
Refluxing right lower-pole ureter
Bladder filled with contrast
Right lower-pole renal pelvis
Orifice of left ureter
Orifice of right lower-pole ureter (prone to reflux)
Ectopic orifice of right upper-pole ureter (prone to obstruction)
F. Netter M.D.

URETERAL DUPLICATION

As shown in Plate 2-1, the ureteric buds appear toward the caudal ends of the mesonephric ducts at 5 weeks of gestation. Each bud grows into its adjacent mass of metanephric mesenchyme, the precursor of the kidney, to form a ureter, a pelvicalyceal system, and collecting ducts.

Ureteral duplication results from abnormalities of the ureteric bud. It is one of the most common congenital malformations of the urinary tract, with an incidence of approximately 1 in 125. Duplication is more often unilateral than bilateral, and more often incomplete than complete. There does not appear to be any predilection for a particular side.

COMPLETE URETERAL DUPLICATION

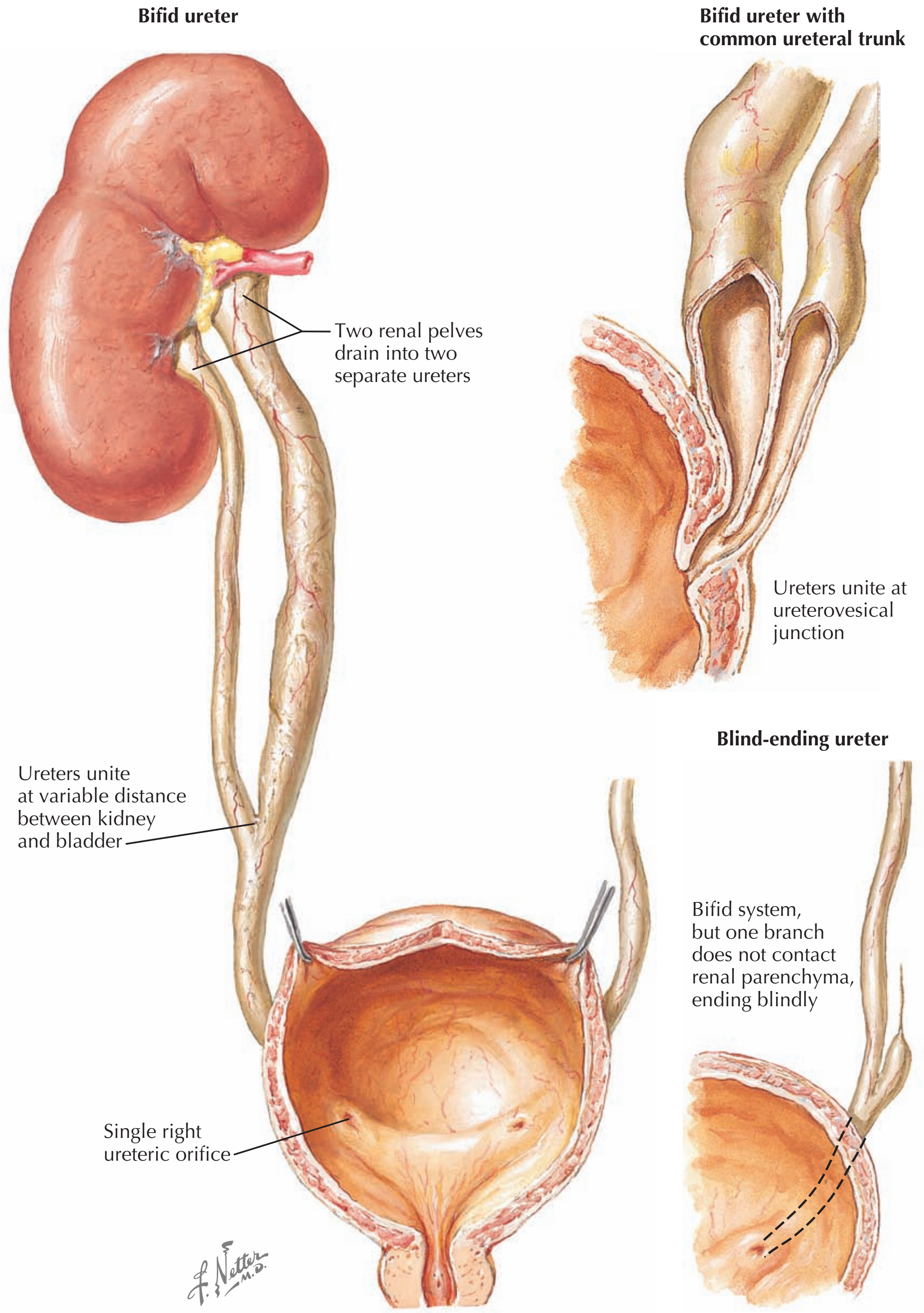
In complete ureteral duplication, the kidney is drained by two distinct renal pelves, each of which leads to a ureter with its own insertion into the bladder. This anomaly occurs when a single mesonephric duct sprouts two ureteric buds, each of which induces a separate portion of the adjacent metanephric mesenchyme. The more cranial of the two ureteric buds becomes the collecting system of the upper pole, while the more caudal of the ureteric buds becomes the collecting system of the lower pole. Because of the manner in which the mesonephric ducts exstrophy into the bladder; however, the upper pole ureter terminates at an orifice located inferior and medial to that of the lower pole ureter. In many cases, the upper pole ureter has an ectopic site of termination, reflecting an especially cranial position of the ureteric bud from which it originated. The consistent pattern of ureteral crossing seen in a duplicated system, where the ureter serving the upper pole terminates inferior to the ureter serving the lower pole, is known as the Weigert-Meyer law.

The upper-pole collecting system tends to serve about one third of the renal parenchyma. The upper pole ureter generally has a long course within the bladder wall, frequently has an ectopic site of termination, and is also prone to ureterocele. Because of these factors, upper pole obstruction and hydroureteronephrosis is common.

Meanwhile, the lower pole ureter tends to have a short course within the bladder wall because of its superior and lateral site of termination. As a result, it is prone to vesicoureteral reflux (VUR, see Plate 2-21), which can cause lower pole hydronephrosis if severe.

Complete ureteral duplication may be detected using various imaging techniques, including intravenous pyelography, ultrasound, CT, and renal scanning. A classic finding is known as the "drooping lily" sign. It consists of downward and lateral rotation of the lower pole segment by an obstructed, hydronephrotic, poorly functioning (and thus nonopacified) upper pole segment. If the lower pole reflux is marked enough, the drooping lily sign may be seen on voiding cystourethrogram (VCUG).

INCOMPLETE URETERAL DUPLICATION


Bifid ureter

Bifid ureter with common ureteral trunk

Blind-ending ureter

Two renal pelves drain into two separate ureters
Ureters unite at variable distance between kidney and bladder
Single right ureteric orifice
Ureters unite at ureterovesical junction
Bifid system, but one branch does not contact renal parenchyma, ending blindly

URETERAL DUPLICATION

(Continued)

INCOMPLETE URETERAL DUPLICATION

Several different patterns of incomplete ureteral duplication may be seen, reflecting various embryologic anomalies. Unlike completely duplicated ureters, incompletely duplicated ureters rarely cause obstruction, VUR, or other sequelae. As a result, they are generally asymptomatic and discovered as incidental findings.

A bifid ureter, or "Y ureter," occurs when one ureteric bud arises from the mesonephric duct but divides before entering the metanephric mesenchyme. As a result, the upper and lower poles are drained by different renal pelves, but the associated ureters fuse before the ureterovesical junction.

The site of ureteral fusion can occur at any distance from the bladder. In some cases, the ureters do not fuse until the ureterovesical junction, where they form a short common ureteral trunk.

A blind-ending ureter is a rarer kind of incomplete duplication. As with a bifid ureter, this anomaly reflects early division of a single ureteric bud; however, in this case, one of the ureteric bud branches fails to induce a portion of metanephric mesenchyme. As a result, a bifid ureter is seen, but one branch does not drain any renal parenchyma and is thus blind-ending. For unknown reasons, blind-ending ureters occur three times more often in women and are more often found on the right side.

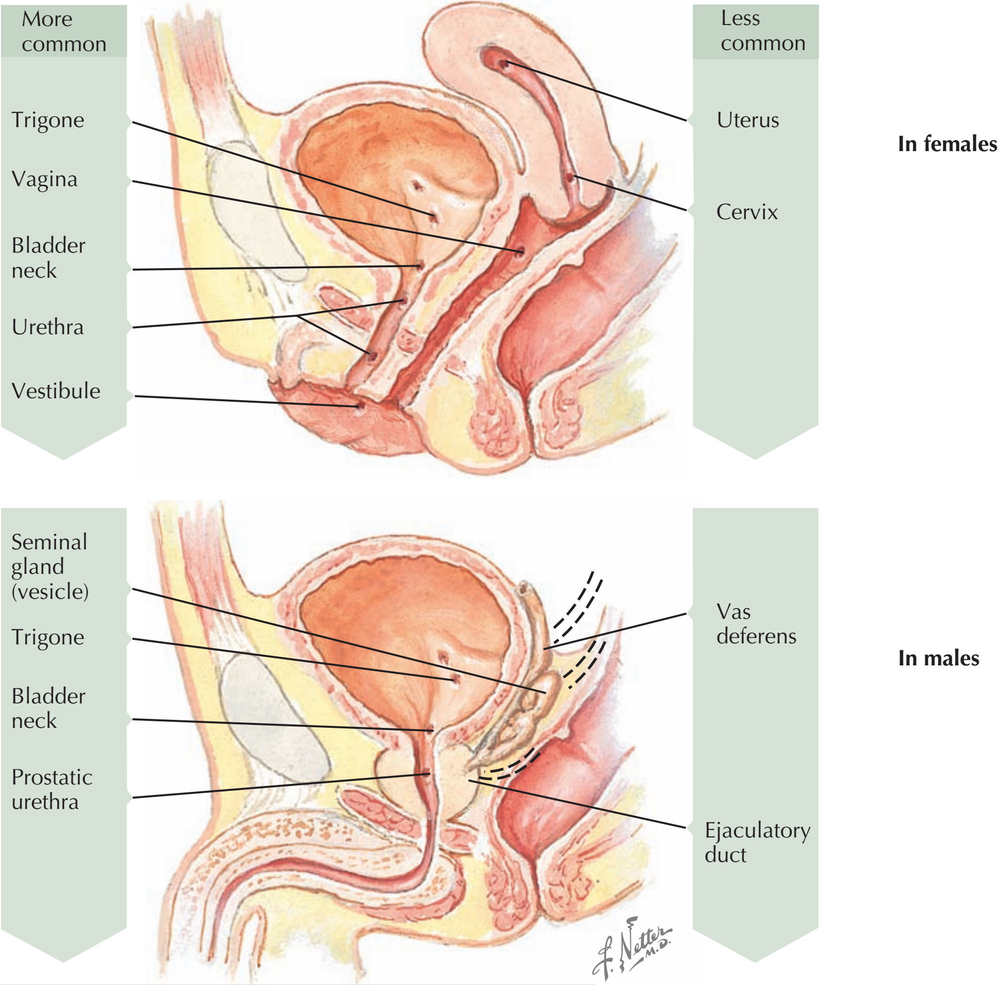
The blind-ending ureteral branch typically terminates adjacent to the distal or middle section of the normal branch. It contains all of the normal layers of the ureteral wall, and it terminates either as a dilated bulb or as an atretic stalk.

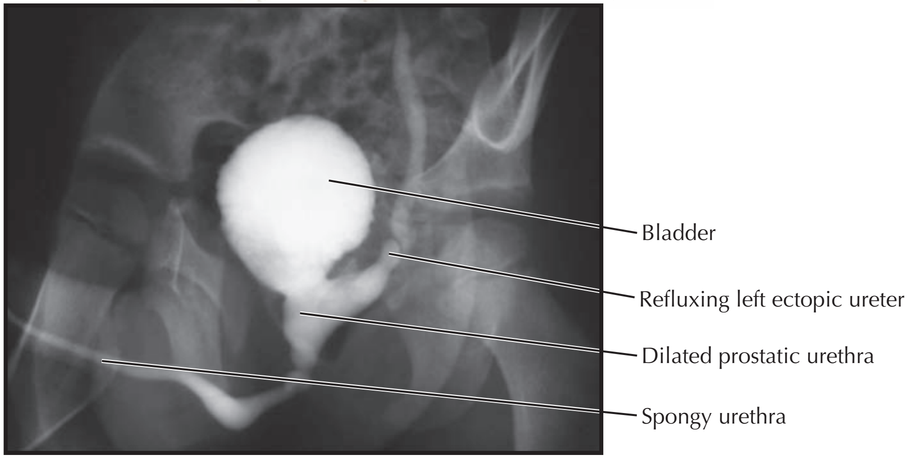
Because the blind-ending ureter does not drain renal parenchyma, it cannot be seen on excretory studies, such as intravenous pyelogram or contrast-enhanced CT. As a result, retrograde studies are generally required to establish the diagnosis.

An "inverted Y" ureter is the rarest form of incomplete duplication. It occurs when two ureteric buds appear on the mesonephric duct but fuse before reaching the metanephric mesenchyme. As a result, a single renal pelvis is seen, but the ureter divides as it approaches the bladder, such that two distinct ureteric orifices are seen on the affected side. One of the ureteral branches often has an ectopic orifice or forms a ureterocele, resulting in obstruction.

ECTOPIC URETER

Observed sites of ectopic ureteric orifices





Voiding cystourethrogram

An ectopic ureter terminates caudal to the normal position in the trigone. Although a ureter that terminates cranial to the normal position is clearly abnormal, and is often associated with vesicoureteral reflux (see Plate 2-21), the term "ectopic" is generally not applied.

In males, the most common sites of ureteral ectopia are the prostatic urethra and seminal glands (vesicles), whereas in females, the most common sites are the urethra and vagina. The incidence of ectopic ureter is not known with precision, although one series estimated it at 1 in 1900. The condition is at least twice as common in females than in males, for unknown reasons.

PATHOGENESIS

As described on page 30, the ureteric buds appear toward the caudal ends of the mesonephric ducts during the fifth week of gestation. Each ureteric bud grows into the adjacent mass of metanephric mesenchyme, the precursor of the kidney, to form a ureter, a pyelocalyceal system, and collecting ducts.

During the sixth week, each mesonephric duct undergoes a process known as exstrophy, in which its most caudal end everts into the primitive bladder and draws in the attached ureter. After the ureters enter the bladder, they separate from the mesonephric duct and attach to the posterior bladder wall. At the end of this process, the ureters normally terminate at orifices located at the superolateral corners of the trigone.

If, however, a ureteric bud is in a more cranial position on the mesonephric duct, the ureter is drawn farther than usual into the bladder during mesonephric duct exstrophy. As a result, the ureteric orifice may appear in a more inferior and medial position, such as at the bladder neck or urethra. If the ureteric bud is even more cranial on the mesonephric duct, the ureter may not be drawn into the bladder at all, instead remaining attached to the mesonephric duct. In males, the ureter may consequently terminate in any of the mesonephric duct derivatives, which include the seminal glands (vesicles), vas deferens, or epididymis. In females, the ureter may end in vestigial mesonephric duct derivatives, such as the epoöphoron and paroöphoron, and then become incorporated into adjacent structures, such as the vagina, uterus, and uterine (fallopian) tubes.

Ectopic ureters are usually seen as part of a duplicated collecting system (see Plate 2-23), in which the affected side has one ureter with a normally positioned orifice and another with an ectopic orifice. This association is logical because complete ureteral duplication occurs when a single mesonephric duct sprouts two ureteric buds, one of which must be in an abnormal position. Ectopic ureters are also frequently associated with renal hypoplasia or dysplasia because the abnormally positioned ureteric bud fails to induce normal differentiation of the metanephric mesenchyme.

PRESENTATION AND DIAGNOSIS

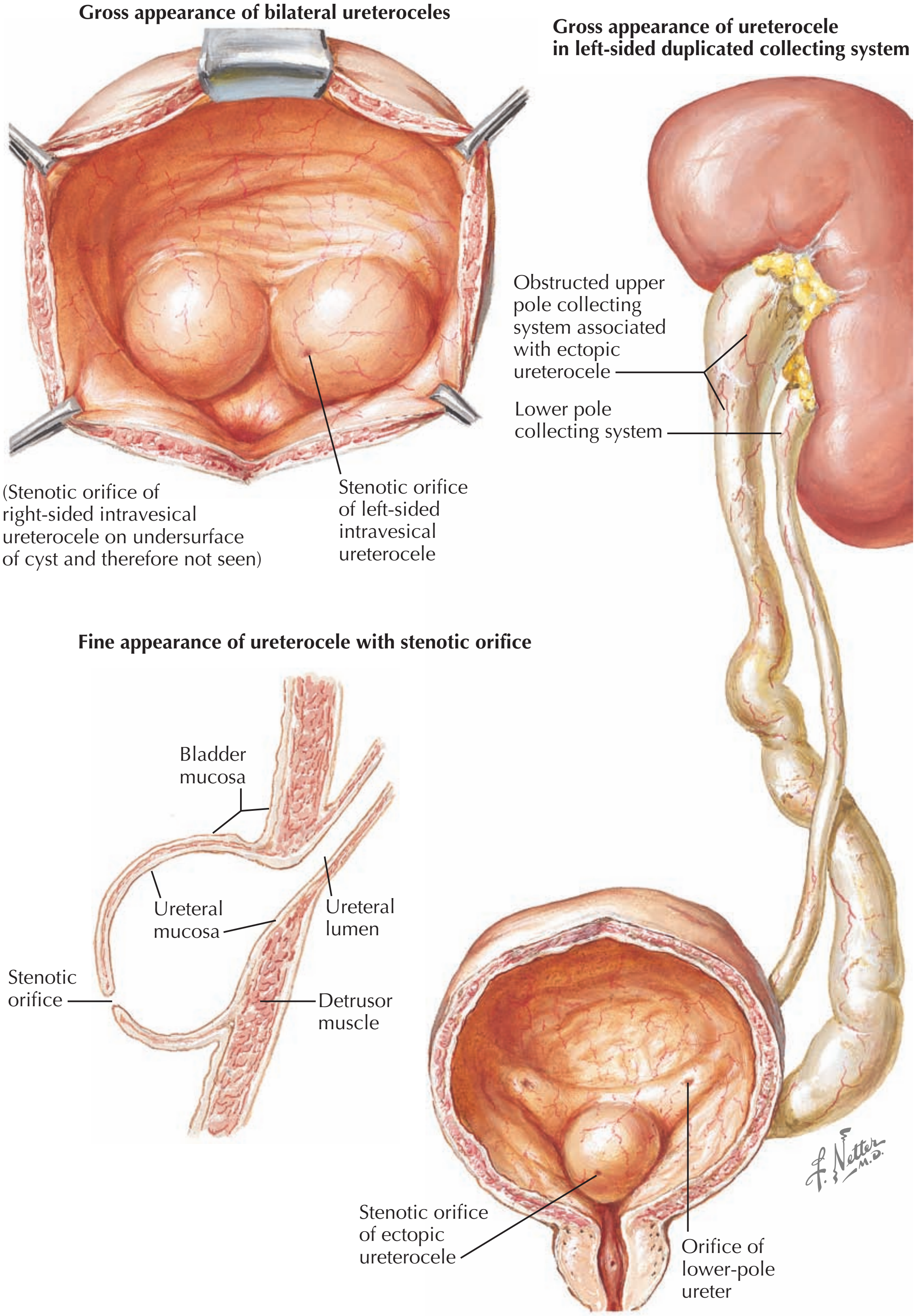
Ectopic ureters may or may not be symptomatic. In males, the common sites of ectopia are all located proximal to the external urethral sphincter, and thus incontinence is not seen. An insertion into the prostatic urethra, however, may lead to urinary frequency and sensations of urgency. Reflux into the ectopic ureteric orifice is often present, and thus upper tract infection may occur. Likewise, an insertion into the epididymis may cause epididymitis. In females, many of the common sites of ectopia are located distal to the external urethral sphincter. Thus many females have constant urine dribbling despite otherwise normal voiding patterns. In both sexes, an ectopic ureter can become obstructed, causing flank pain or even a palpable mass.

An ectopic ureter may initially be seen on ultrasound, either with or without associated renal (hypo)dysplasia. If there is ureteral obstruction, hydroureteronephrosis will be seen. If an ectopic ureter is suspected, high-resolution axial imaging or a VCUG can often provide additional information. With females, careful cystoscopy, vaginoscopy, and inspection of the urethrovaginal septum may even provide direct visualization of the ectopic ureteric orifice. In males, careful cystoscopy and examination under anesthesia may also be diagnostic. Once an ectopic ureter has been identified, a renal scan should be performed to assess the function of the associated renal parenchyma.

TREATMENT

Because ectopic ureters are often associated with dysplastic kidneys, the treatment usually consists of nephroureterectomy or, in the case of a duplicated collecting system, heminephrectomy. If, in contrast, the renal parenchyma associated with the ectopic ureter appears to be functional, or if there are bilateral ectopic ureters, ureteropyelostomy or ureteral reimplantation can be performed instead.

GROSS AND FINE APPEARANCE OF URETEROCELE



Gross appearance of bilateral ureteroceles

Gross appearance of ureterocele in left-sided duplicated collecting system

Fine appearance of ureterocele with stenotic orifice

(Stenotic orifice of right-sided intravesical ureterocele on undersurface of cyst and therefore not seen)
Stenotic orifice of left-sided intravesical ureterocele
Obstructed upper pole collecting system associated with ectopic ureterocele
Lower pole collecting system
Bladder mucosa
Ureteral mucosa
Ureteral lumen
Stenotic orifice
Detrusor muscle
Stenotic orifice of ectopic ureterocele
Orifice of lower-pole ureter
F. Netter M.D.

URETEROCELE

A ureterocele is a cystic dilation of the terminal ureter that balloons into the bladder. About 80% of ureteroceles are associated with ureteral duplication, occurring in the ureter that drains the upper pole (see Plate 2-23). About 10% of ureteroceles are bilateral.

A ureterocele is known as "intravesical" if it extends only into the bladder, and "ectopic" if it reaches the bladder neck or urethra. The orifice is termed "stenotic" if a pinpoint opening is seen and "sphincteric" if it lies distal to the bladder neck. If the orifice possesses both of these characteristics, it is known as "sphincterostenotic."

The overall incidence of ureteroceles is difficult to estimate because many small ureteroceles are not identified. The clinical incidence of ureterocele, however, appears to range from 1 in 5000 to 1 in 12,000. In contrast, one autopsy series reported the incidence to be as high as 1 in 500. For unknown reasons, there is a female : male ratio of 4 : 1, and most cases occur in whites.

PATHOGENESIS

The embryologic basis for ureteroceles is unknown, but several theories have been proposed. One is that ureteroceles result from incomplete breakdown of the Chwalla membrane, a normally transient structure that divides the ureter from the bladder. Although this theory explains ureteroceles with stenotic orifices, it does not explain those with patent orifices. Another theory is that the terminal ureter is lined with an inadequate number of smooth muscle cells, which causes it to become dilated.

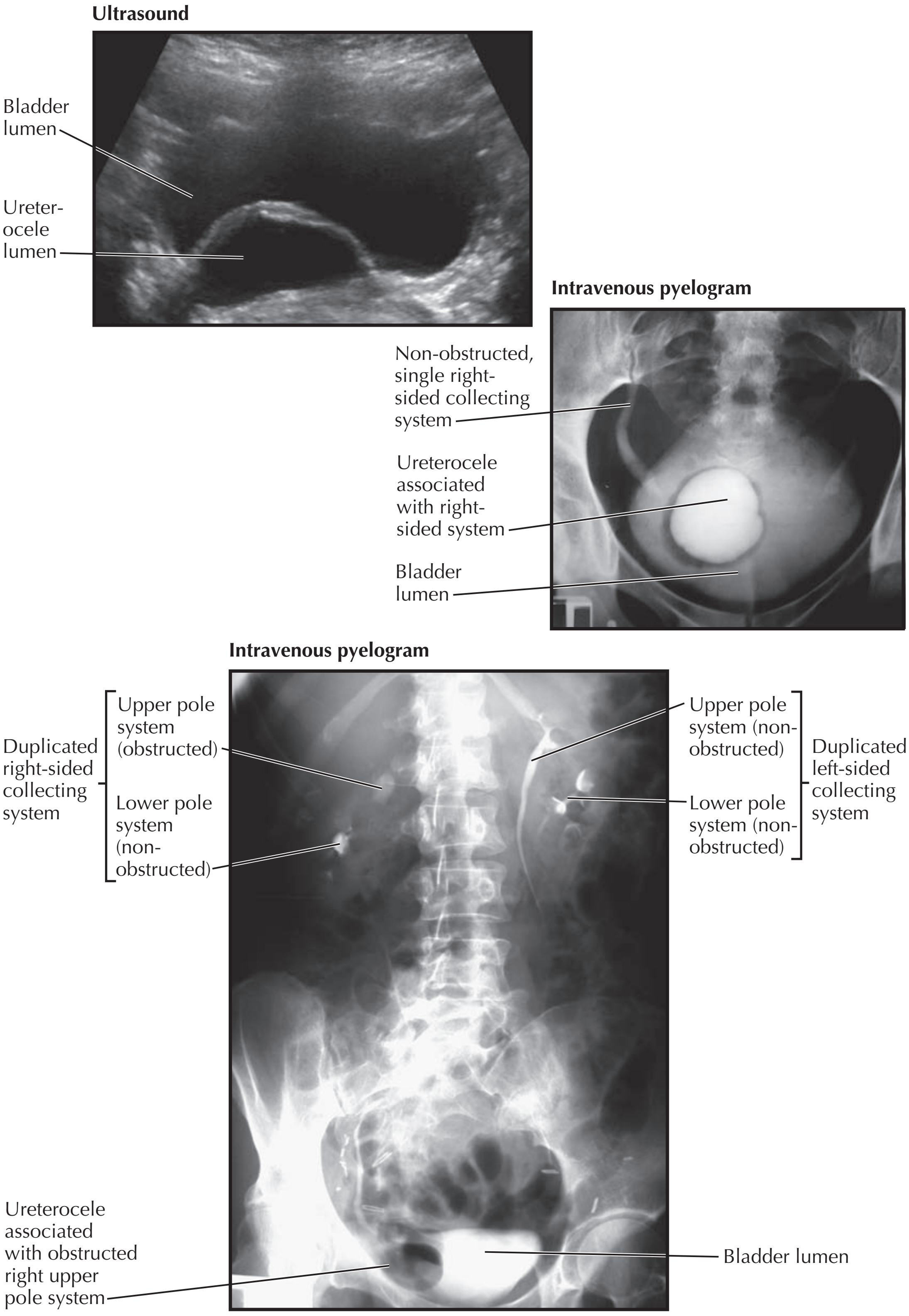
PRESENTATION AND DIAGNOSIS

A ureterocele may be asymptomatic, but it can also cause ureteral obstruction, especially when it is associated with a duplicated system. If large enough, the ureterocele can obstruct the bladder neck or even the contralateral ureteric orifice.

If a ureterocele is not diagnosed using prenatal ultrasound, it may become apparent during infancy. The most common presentation is a urinary tract infection, which results from urinary stasis in the obstructed system. Less often, a ureterocele can cause failure to thrive, flank pain, or hematuria. If the ureterocele lies within the bladder neck, voiding dysfunction may occur. If the obstruction and associated hydronephrosis are severe, the kidney may become a palpable abdominal mass.

The diagnosis of ureterocele is typically established using ultrasound. In most cases, ureteral duplication is also seen. Hydroureteronephrosis may be seen if there is an obstruction. The diagnosis may be missed if the bladder is overdistended with urine because the

RADIOGRAPHIC FINDINGS OF URETEROCELE


Ultrasound
Bladder lumen
Ureterocele lumen
Intravenous pyelogram
Non-obstructed, single right-sided collecting system
Ureterocele associated with right-sided system
Bladder lumen
Intravenous pyelogram
Duplicated right-sided collecting system
Upper pole system (obstructed)
Lower pole system (non-obstructed)
Upper pole system (non-obstructed)
Lower pole system (non-obstructed)
Duplicated left-sided collecting system
Ureterocele associated with obstructed right upper pole system
Bladder lumen

URETEROCELE *(Continued)*

ureterocele may become effaced. In addition, it is important to distinguish between a ureterocele, which is separated from the bladder lumen by its own thin wall, and a dilated ectopic ureter, which is separated from the bladder lumen by the thicker bladder walls.

A VCUG is helpful for further characterizing the size and location of a ureterocele, which becomes visible as a discrete, smooth filling defect near the trigone. In duplicated systems, the ipsilateral lower pole ureter often exhibits vesicoureteral reflux. The reflux is related both to the short intramural course of the lower pole ureter (see Plate 2-21) and to the deforming effect of the ureterocele on the trigone. In rare cases, the ureterocele itself may exhibit reflux. Again, it is essential to obtain images during early bladder filling because high intravesical pressures can cause the ureterocele to become effaced.

An intravenous pyelogram or contrast-enhanced CT can also be performed to characterize a ureterocele. An obstructed ureterocele that is associated with a poorly functional renal unit, as often seen in a duplicated system, will not fill with contrast and will appear as a filling defect in the bladder. In contrast, a nonobstructed ureterocele associated with a functional renal unit, as may be seen in a nonduplicated system, will fill with contrast. The ureterocele wall will then form a visible halo in the bladder.

If the ureterocele is large, it may be difficult to determine from which side it originates. In such cases, it is helpful to directly visualize the ureterocele using a cystoscope; intubate it with a ureteral catheter and perform a retrograde pyeloureterogram, generally at the same time that definitive repair is planned.

TREATMENT

Once a ureterocele has been identified, the patient should be started on antibiotic prophylaxis to reduce the risk of urinary tract infection. In addition, a radionuclide renal scan should be performed to determine the functional status of the associated renal parenchyma, especially if there is a duplicated system, because the results will determine the optimal surgical approach.

The goals of surgical intervention include relief of obstruction, infection, and reflux. The standard options include endoscopic incision of the ureterocele, as well as various open or laparoscopic procedures, such as heminephrectomy, ureteropyelostomy, ureteroureterostomy, and ureteral implantation.

It is impossible to offer a simple algorithm for the management of ureteroceles. In each case, the plan must take into account numerous variables, including patient age, the size and position of the ureterocele, history of urinary tract infections, the presence or absence of reflux, the presence of a single or duplicated collecting system, and the degree of function in the associated renal parenchyma.

PRUNE BELLY SYNDROME

The prune belly syndrome (PBS, also known as Eagle-Barrett or triad syndrome) is a rare, congenital disorder that occurs almost exclusively in males. Its major features include deficient abdominal wall musculature, bilateral cryptorchidism, and urinary tract anomalies that include renal dysplasia, hydronephrosis, and dilation of the ureters and bladder.

PBS occurs in approximately 3.5 per 100,000 live male births. Blacks are at increased risk and Hispanics are at decreased risk when compared with the overall population. There are rare reports of females born with deficient abdominal wall musculature and urinary tract anomalies, although their ovaries are generally normal.

PATHOGENESIS

The pathogenesis of PBS remains poorly understood. One theory argues that early obstruction of the bladder outlet causes dilation of the bladder, ureters, and then renal pelves. Such dilation is posited to cause an increase in intraabdominal pressure that results in atrophy of the abdominal wall musculature and inhibition of normal testicular descent. This hypothesis, however, is challenged by the fact that many patients with PBS do not have an anatomic outlet obstruction, and that many patients who do have such obstructions (such as those with posterior urethral valves) do not have PBS.

Another theory argues that the primary defect lies in the intermediate and lateral plate mesoderm, which gives rise to the urinary tract, genital tract, and abdominal wall musculature (see Plate 2-1). The causes and nature of the mesodermal defect, however, remain unknown. Because 1 in 23 children with prune belly syndrome is the product of a twin pregnancy, however, at least some cases could reflect an uneven distribution of mesoderm between twinned embryos early in gestation.

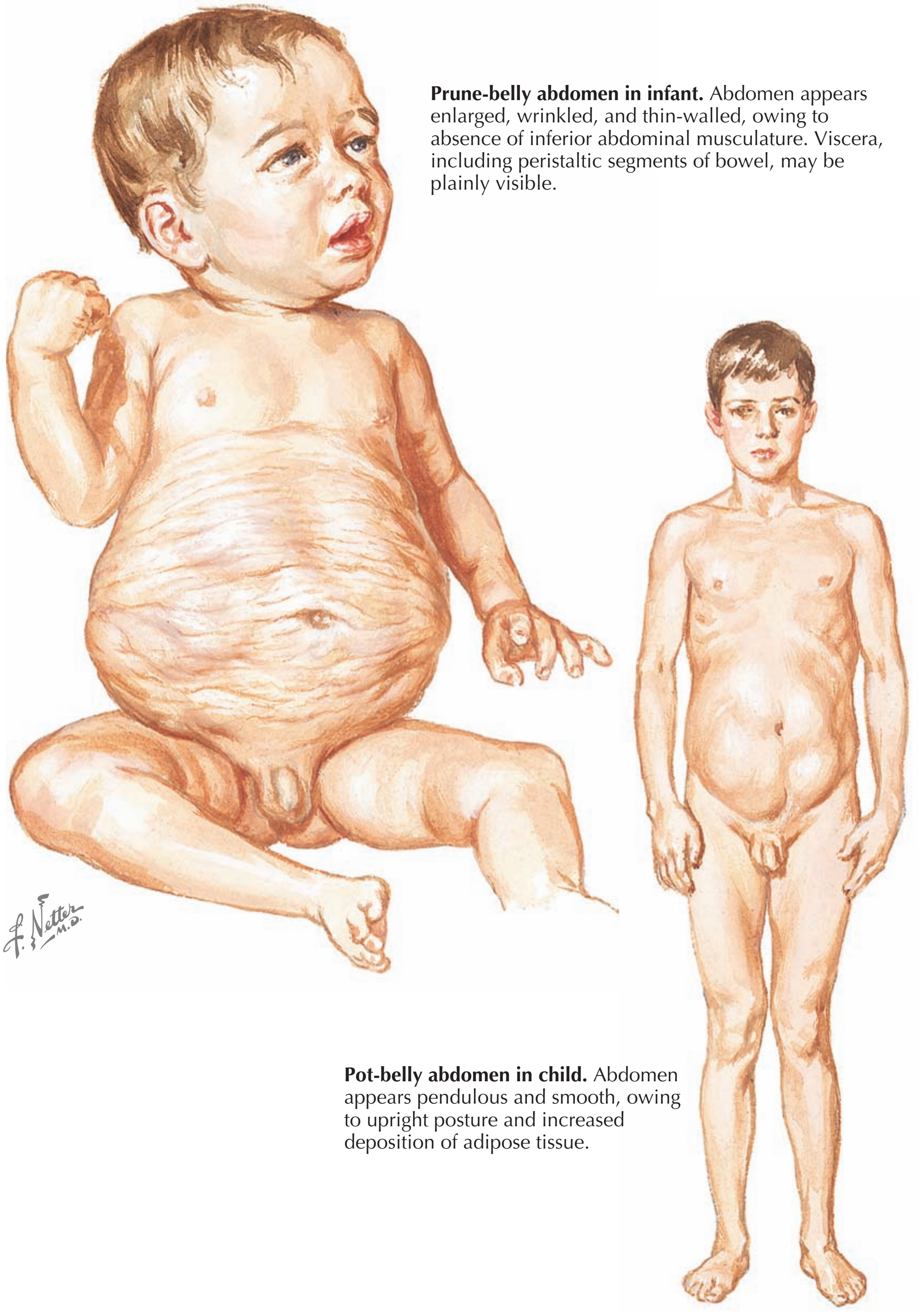
The genetics of PBS also remain poorly understood. Although most cases are sporadic, a small number of familial cases have been reported and suggest a sex-linked autosomal recessive pattern of inheritance. Most affected infants possess normal karyotypes, but some associations have been noted with trisomies 13, 18, and 21.

PRESENTATION AND DIAGNOSIS

PBS can often be detected using prenatal ultrasound, which has been shown to establish the diagnosis as early as 11 weeks into gestation. Suggestive findings include hydronephrosis, bladder enlargement, and absence of the abdominal musculature. If there is severe renal dysplasia or a bladder outlet obstruction, oligohydramnios and pulmonary hypoplasia may also be seen.

If PBS is not diagnosed in the antenatal period, it is generally readily apparent at birth. The most striking feature of affected infants is the wrinkled, prunelike skin overlying their inferior abdominal wall, which reflects attenuation or outright absence of the normal abdominal musculature. The abdominal wall may be so thin that the underlying organs, including peristaltic regions of the bowel, become visible. As affected children grow older and spend more time standing upright, the wrinkles become less prominent, and the abdomen assumes a "pot-bellied" appearance. The lack of abdominal musculature makes it difficult for affected patients to sit upright from a supine position. Some reports have also suggested that it increases the risk of pneumonia by impairing the normal coughing mechanism, and that it can cause constipation by preventing the generation of increased intraabdominal pressure.

APPEARANCE OF ABDOMINAL WALL IN PRUNE BELLY SYNDROME



Prune-belly abdomen in infant. Abdomen appears enlarged, wrinkled, and thin-walled, owing to absence of inferior abdominal musculature. Viscera, including peristaltic segments of bowel, may be plainly visible.

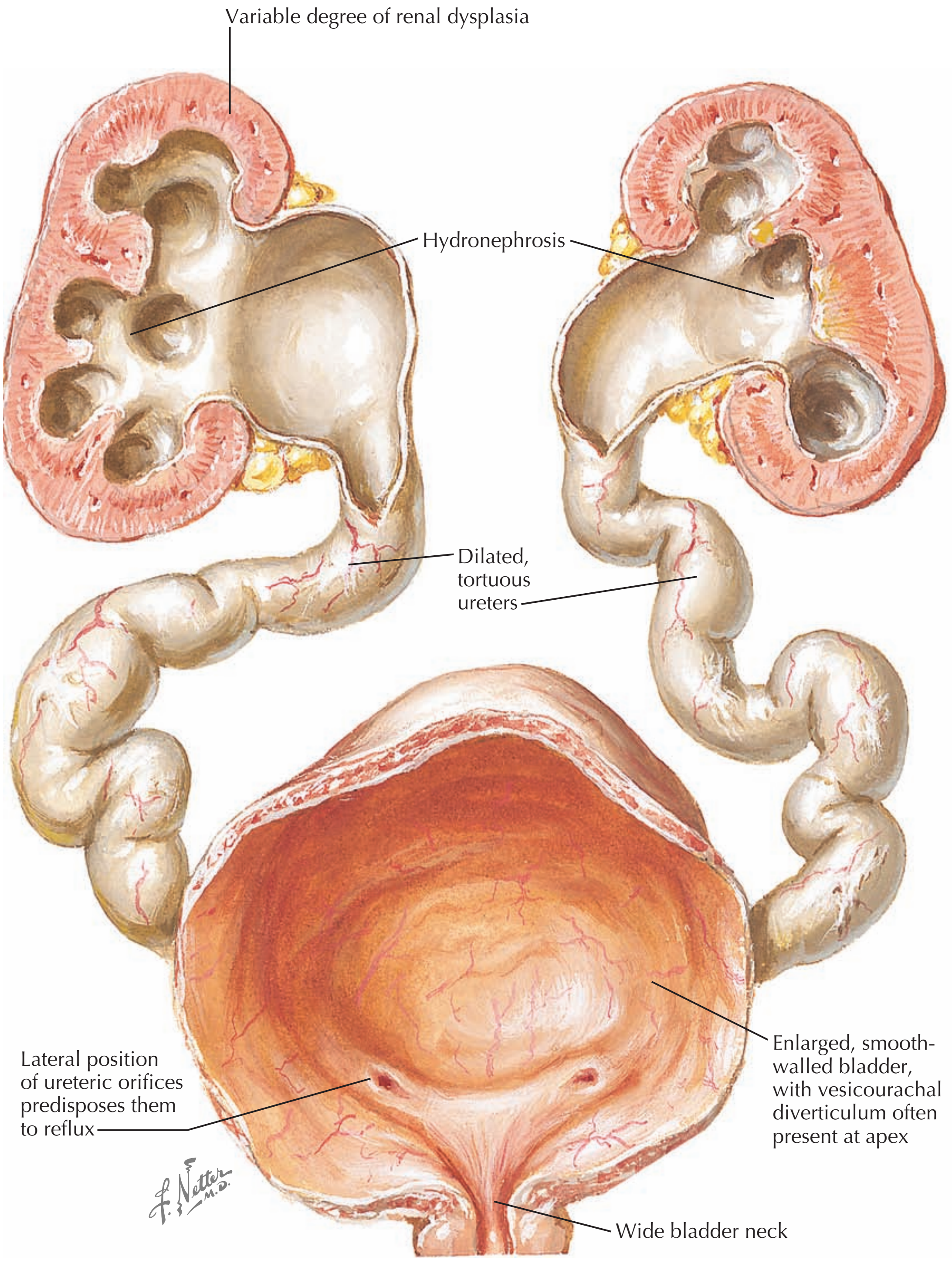
Pot-belly abdomen in child. Abdomen appears pendulous and smooth, owing to upright posture and increased deposition of adipose tissue.

Although all patients have hydronephrosis, the degree of renal dysplasia is variable and has important prognostic implications. Those with the most severe renal dysplasia develop the Potter sequence (Plate 2-8) and typically succumb to severe respiratory distress shortly after birth. Those with moderate dysplasia often develop end-stage renal disease (ESRD) during childhood. Finally, those with minimal or no dysplasia often maintain normal or near-normal renal function. To assess for renal abnormalities, an ultrasound should be performed in the neonatal period, and serial measurements of the serum creatinine concentration should be obtained (recognizing that early values reflect maternal, rather than neonatal, renal function). If there is evidence of renal dysfunction, a renal scan can provide more detailed functional information.

The ureters appear broad and tortuous, especially as they approach the bladder, and peristalsis is weak and ineffective. These anomalies reflect a relative lack of smooth muscle cells in the ureteral walls, which instead

Prune Belly Syndrome
(Continued)

Appearance of Kidneys, Ureters, and Bladder in Prune Belly Syndrome


Variable degree of renal dysplasia
Hydronephrosis
Dilated, tortuous ureters
Enlarged, smooth-walled bladder, with vesicourachal diverticulum often present at apex
Lateral position of ureteric orifices predisposes them to reflux
Wide bladder neck
F. Netter M.D.

consist primarily of fibrous connective tissue. In addition, the ureteric orifices are often at abnormally lateral positions, which predisposes them to reflux.

The bladder appears enlarged, with a vesicourachal diverticulum often present. The bladder wall appears smooth and thick secondary to increased collagen deposition. The detrusor muscle is hypoplastic, which may cause weak bladder contractions associated with large postvoid residuals. The combination of urinary stasis in the bladder, which increases the risk of bacterial infection, and vesicoureteral reflux, which permits passage of infected urine into the renal pelves, may lead to recurrent pyelonephritis and progressive worsening of renal function. Thus if there is evidence of bladder dysfunction, a VCUG should be performed after sufficient antibiotic prophylaxis has been provided.

The bladder neck and prostatic urethra appear widened, with the latter resulting from prostatic hypoplasia. The prostatic urethra tapers to the membranous urethra, resulting in an inverted triangle appearance on VCUG. The anterior urethra is typically normal. A small subset of patients may have urethral dilation (megalourethra) owing to absence of either the corpora spongiosum alone or, in rare cases, both the corpora spongiosum and cavernosum. An even smaller number of patients have complete urethral atresia, resulting in oligohydramnios and Potter sequence.

The testes are generally located in the abdomen, near or above the iliac vessels. They appear histologically abnormal, with a reduced number of spermatogonia, and are at increased risk for malignancy. The combination of testicular dysfunction and prostatic hypoplasia renders patients infertile. In addition, retrograde ejaculation is common because of the open bladder neck.

Other organ systems show a variable degree of involvement. Cardiac anomalies, seen in 10% to 20% of patients, include septal defects and patent ductus arteriosus. Pulmonary anomalies include pulmonary hypoplasia, which occurs in those with Potter sequence, as well as pneumothorax. Early assessment for cardiopulmonary anomalies, including a chest radiograph, is thus an important component of the postnatal evaluation. Finally, gastrointestinal complications range from constipation, which occurs in most patients, to serious anomalies such as intestinal malrotation or anorectal malformations.

TREATMENT

Because recurrent pyelonephritis is common and can lead to renal scarring, lifelong antibiotic prophylaxis should be started during the postnatal period. In addition, urine cultures and measurements of the serum creatinine concentration should be obtained on a regular basis.

If bacterial infections continue to occur, or if renal function appears to be deteriorating, the abnormal collecting system may be reconstructed. The ureters are tapered and reimplanted to reduce reflux. In addition, a reduction cystoplasty, which consists of excision of the vesicourachal diverticulum or other redundant areas of mucosa, may be performed to reduce the volume of retained urine. Although the majority of patients empty their bladders adequately, a subset require clean intermittent catheterization.

Abdominal wall reconstruction can mitigate the psychological effects of PBS, and it may also improve constipation and reduce the risk of pneumonia. The most popular technique, known as the Monfort procedure, consists of an elliptical incision to remove redundant skin, a second incision around the umbilicus so that it can remain in position, and two vertical incisions through the abdominal fascia to overlap redundant segments and increase the strength of the abdominal wall.

Finally, early orchidopexy is recommended in all patients because it often allows them to achieve normal production of sex hormones at puberty. In addition, it greatly facilitates a regular examination for testicular malignancies.

The prognosis of patients with PBS who survive the postnatal period depends primarily on the severity and progression of renal dysfunction. Unfortunately, even those who survive infancy with mild renal impairment may progress to renal failure due to recurrent pyelonephritis, particularly in patients who incompletely empty their bladders. Renal transplantation has been shown to be a feasible option for these patients.

Epispadias Exstrophy Complex

The exstrophy-epispadias complex encompasses a spectrum of disorders thought to represent increasingly severe defects in infraumbilical midline development. There is invariable involvement of the urinary tract and genitalia, and there may also be involvement of the abdominal wall, anus, pelvis, and spine. The timing and nature of the underlying embryologic defect are thought to determine which structures are involved, and thus which condition in the complex will result. In order of increasing severity and multisystem involvement, the conditions in the complex are known as epispadias, bladder exstrophy, and cloacal exstrophy.

CLASSIFICATION

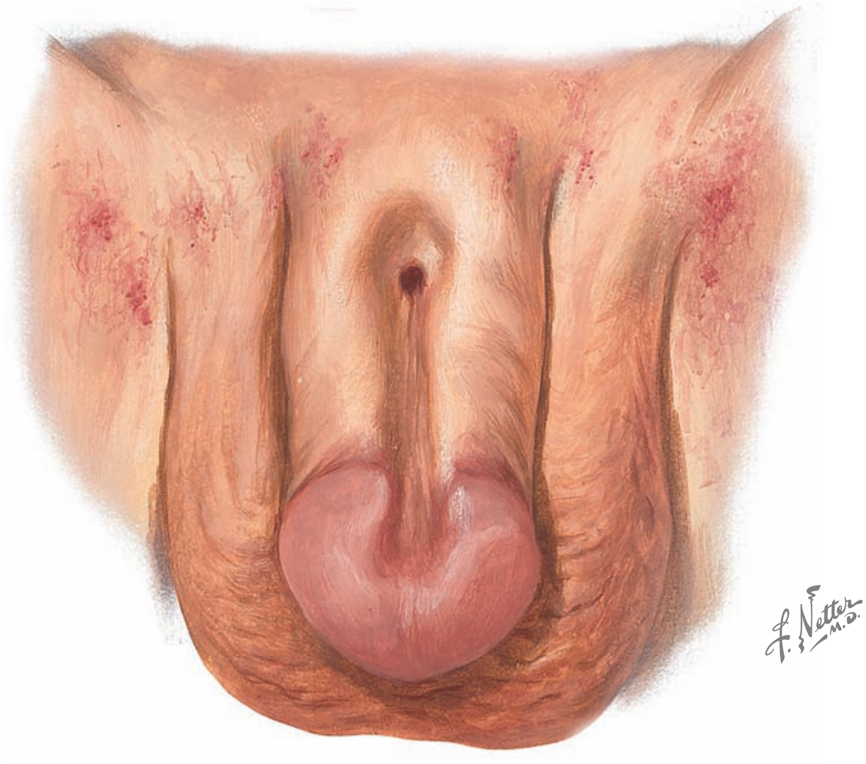
Epispadias, the least severe condition, features an open defect in the dorsal wall of the urethra. As a result, the urethra becomes a flat strip of exposed mucosa. In males, this strip begins at the external meatus and continues proximally either to the base of the glans (balanic epispadias), base of the penis (penile epispadias), or bladder neck (penopubic epispadias). In penopubic epispadias, the defect usually leads to absence of the normal sphincter mechanisms, resulting in urinary incontinence. In females, the dorsal urethral defect may likewise be short, resulting in a patulous urethral orifice, or more extensive, causing an open defect that reaches the neck of the bladder.

Bladder exstrophy is a more severe condition in which there is failed closure of the anterior abdominal wall in the midline. In addition, there are multiple abnormalities of the bony pelvis, including a wide pubic diastasis. The umbilicus is low set and marks the cranial extent of the abdominal wall defect, whereas the anus is anteriorly displaced and marks the caudal end of the defect. The anterior wall of the bladder is absent, and the everted posterior wall of the bladder is exposed through the abdominal wall defect. The ureteric orifices are visible and laterally displaced, with shortened intramural segments. Epispadias is always present. Males have a foreshortened penis, which reflects both a reduction in anterior corpora cavernosal tissue, as well as retraction of cavernosal tissue secondary to the pubic diastasis. Females have a bifid clitoris and foreshortened vagina. Umbilical and indirect inguinal hernias are often present.

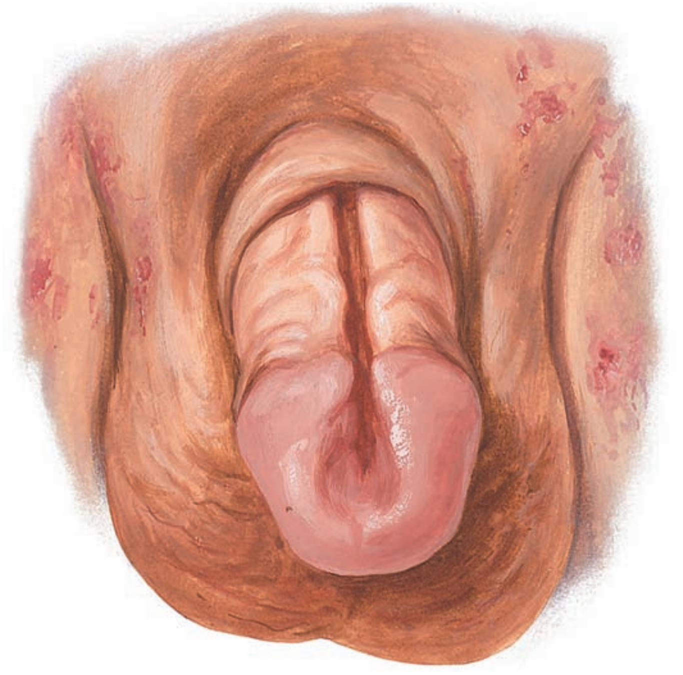
Cloacal exstrophy is the most severe condition in which bladder exstrophy is accompanied by bladder division, exstrophy of the terminal ileum between the two halves of the bladder, a blind-ended hindgut, imperforate anus, omphalocele, complete phallic division (in males), complete vaginal and uterine duplication (in females), and spinal defects.

Bladder exstrophy is the most common of these three anomalies. The incidence is reported to be between 2.1 and 4 per 100,000 births, although it has been declining, likely due to prenatal diagnosis and termination of affected fetuses. There is at least a 2 : 1 male-to-female ratio, with some series reporting an even higher male predilection. Isolated epispadias occurs in approximately 1 in 117,000 males and 1 in 484,000 females. Finally, cloacal exstrophy occurs in 1 in 200,000 to 1 in 400,000 births.

EPISPADIAS



Penile epispadias



Penopubic (complete) epispadias

PATHOGENESIS

The embryologic defect underlying the epispadias-exstrophy complex is poorly understood. The most prominent theory argues that the main defect lies in the cloacal membrane, the bilaminar structure consisting of ectoderm and endoderm that is situated anterior to the cloaca (see Plate 2-3). In normal development, the cloacal membrane occupies a large territory on the ventral surface of the embryo just inferior to the body stalk. As development proceeds, however, mesoderm invades the cranial aspect of the cloacal membrane, interposing itself between the ectoderm and endoderm. This mesoderm, which now occupies the infraumbilical space, fuses in the midline and gives rise to the infraumbilical abdominal wall, pubic rami, and anterior surface of the detrusor muscle. In addition, specialized regions of the mesoderm form the paired genital folds, which fuse in the midline to form the genital tubercle

Epispadias Exstrophy Complex *(Continued)*

(see top left illustration in Plate 2-4). In the meantime, the cloaca undergoes septation into an anterior urogenital sinus and posterior rectum, the orifices of which become exposed following apoptosis of the cloacal membrane.

If the cloacal membrane does not permit mesodermal invasion, midline fusion of the mesodermal structures is not possible, resulting in midline defects of the abdominal wall and pelvis. In cloacal exstrophy, this defect is hypothesized to occur in conjunction with abnormal cloacal septation. As a result, both the bladder and hindgut become exposed through the abdominal wall defect following apoptosis of the cloacal membrane. In addition, the cloacal membrane prevents fusion of the genital folds, causing the genitalia to appear bifid. Meanwhile, in both bladder exstrophy and epispadias, impaired mesodermal invasion occurs in conjunction with normal septation of the cloacal membrane. As a result, the abdominal wall defect exposes either the urethra alone or both the urethra and bladder, depending on its size. In either case, it appears that the genital folds fuse to a large extent at the level of the urorectal septum, caudal to the urogenital sinus. In males, this arrangement would explain the presence of the urethra on the anterior surface of the undivided penis.

PRESENTATION AND DIAGNOSIS

The diagnosis of bladder exstrophy can be established using prenatal ultrasound performed after 15 weeks of gestation. The major findings include poor visualization of the bladder, a lower abdominal bulge, small genitalia (in males), a low-set umbilicus, and a pubic bone diastasis. If the diagnosis is not established before birth, it is readily apparent upon delivery.

TREATMENT

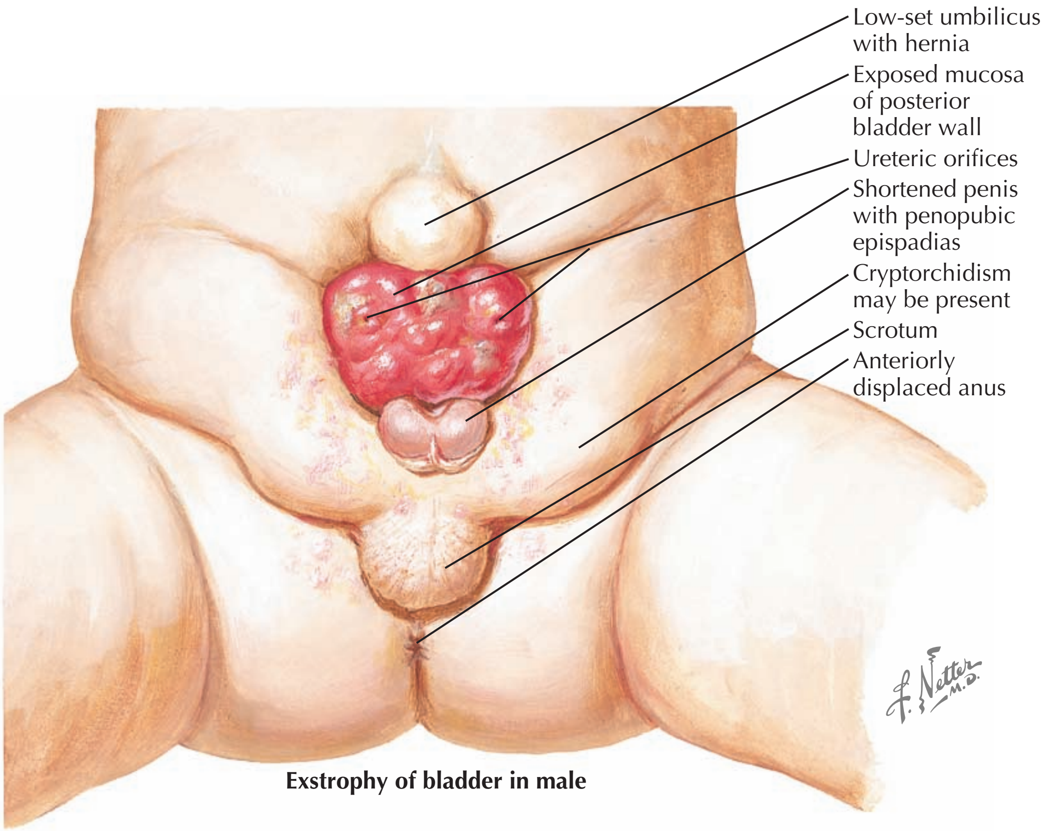
Immediately after birth, the umbilical cord should be tied with a ligature rather than clamped with plastic or metal, so as to minimize trauma to the exposed bladder mucosa. Likewise, a sheet of plastic wrap should be used to cover the anterior abdominal defect and protect the bladder mucosa from abrasion by towels, diapers, and clothing. A thorough physical and radiologic assessment should be performed to assess for the presence of other anomalies.

The relative merits of a single or staged repair of the exstrophy, epispadias, abnormal ureterovesical junctions, and abnormal bladder neck have yet to be determined; however, it is clear that the sooner the exstrophied bladder is closed and the bladder neck and sphincter are reapproximated, the better the chance for a functional bladder and long-term urinary continence.

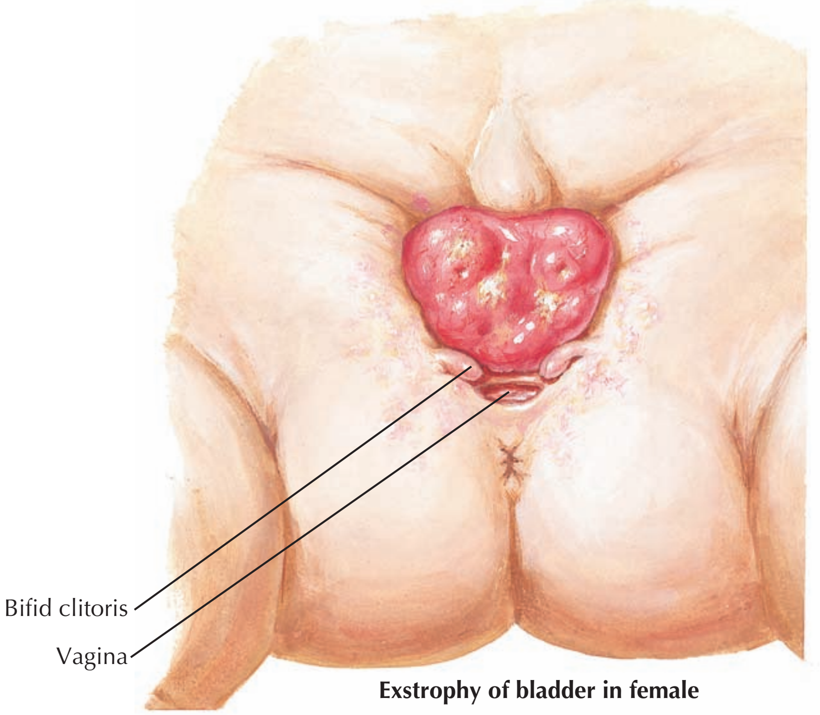
The timing of the initial closure depends on a number of variables, including the size of the bladder, the size of the penis in the male patient, the length and depth of the urethral groove, the width of the pubic diastasis, and the presence or absence of other associated anomalies. Most exstrophies, however, can be closed within the first 72 hours of the infant's life, which protects the bladder mucosa from the environment and facilitates development of the bladder musculature. At the time of the initial closure, many patients also undergo pelvic osteotomy in which the ilia and ischia are cut to facilitate reapproximation of the pubic symphysis. This procedure can reduce tension on the abdominal wall closure, and it reapproximates the pelvic floor musculature in the midline to improve later continence. Whether osteotomy is performed or not, the infant's pelvis is usually immobilized for up to 1 month after the procedure to facilitate normal bone alignment.

With current reconstructive strategies, most patients achieve urinary continence (albeit with clean intermittent catheterization in a significant proportion) and can lead satisfying personal and professional lives. Long-term management, however, must address the psychological effects of this condition, possible sexual dysfunction (especially in women), and later complications, such as vaginal and rectal prolapse in women.

Bladder Exstrophy


Low-set umbilicus with hernia
Exposed mucosa of posterior bladder wall
Ureteric orifices
Shortened penis with penopubic epispadias
Cryptorchidism may be present
Scrotum
Anteriorly displaced anus

Exstrophy of bladder in male



Exstrophy of bladder in female

BLADDER DUPLICATION AND SEPTATION

Bladder duplication and septation are very rare congenital abnormalities, with only a small number of cases reported in the scientific literature. In either duplication or septation, division of the bladder may be complete or incomplete, and it may occur in the coronal or sagittal plane.

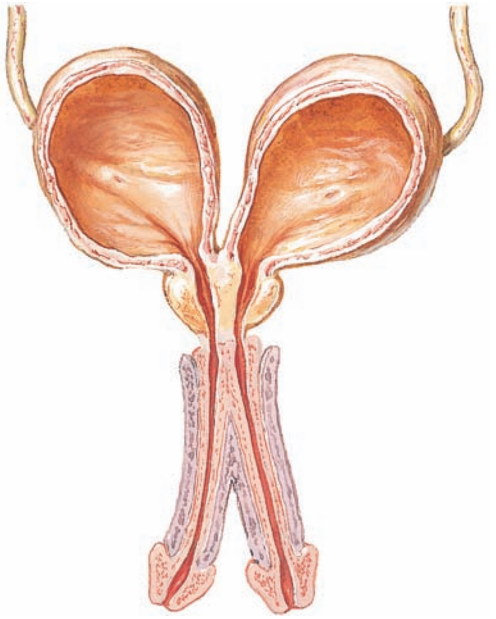
In duplication, each half of the divided bladder receives its own ureter and possesses its own full-thickness wall. In incomplete duplication, the two halves typically unite above the level of the bladder neck and then drain together into a single urethra. In complete duplication, the two halves remain separate to the level of the bladder neck and can even drain into two independent urethras, each with its own external meatus. In some cases, however, one of the bladder halves lacks a urethral component, resulting in outlet obstruction and ipsilateral renal abnormalities.

In septation, a fibromuscular wall divides the bladder into separate compartments. In contrast to duplication, septation produces two compartments that share a common wall. Like duplication, septation can be incomplete or complete, depending on how far the wall extends toward the bladder neck. Septation, however, is not associated with duplication of the urethra, and thus both compartments must be in open communication with the urethra. In some cases, however, fusion of the septum with the bladder neck causes one compartment to lose access to the urethra, resulting in obstruction.

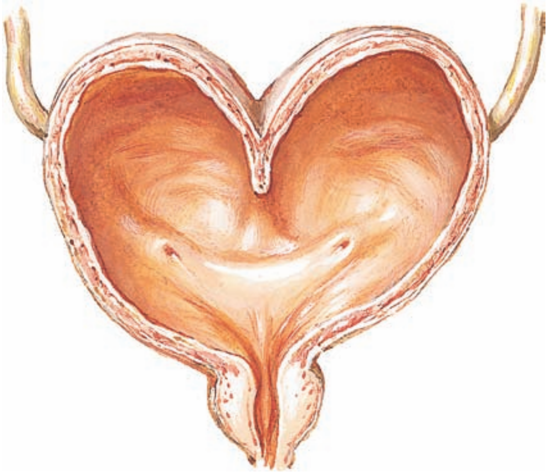
Bladder duplication and septation are frequently associated with other anomalies, especially in the genitourinary system. For example, vesicoureteral reflux may be seen on one or both sides, resulting in hydronephrosis if severe. Likewise, one or both of the bladder components may lack a normal continence mechanism. If there is complete duplication of the bladder, concurrent duplication of the external genitalia may be seen as well. Less often, duplication may also occur in the lower gastrointestinal tract or spine.

PATHOGENESIS

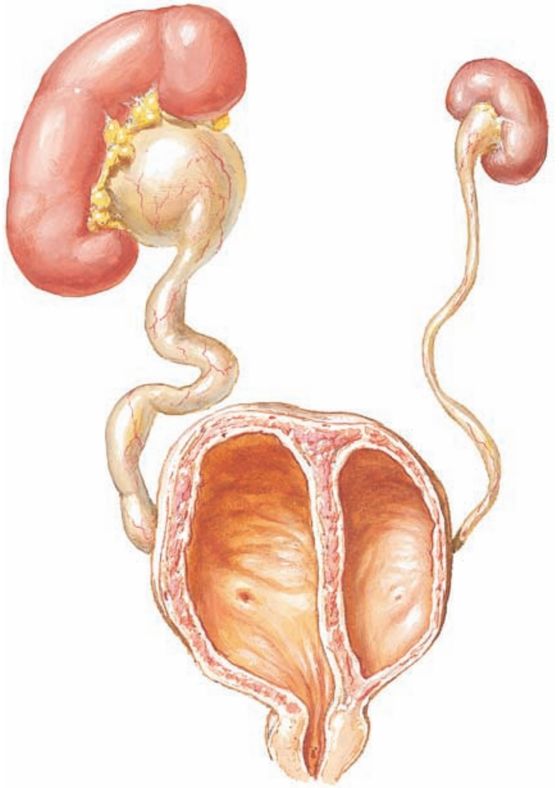
The embryologic basis for these various anomalies is unknown. It is possible that complete duplication of the bladder and adjacent organ systems reflects partial twinning of the embryonic tail early in gestation. In contrast, isolated defects of the bladder may reflect abnormalities during cloacal septation (see Plate 2-4).



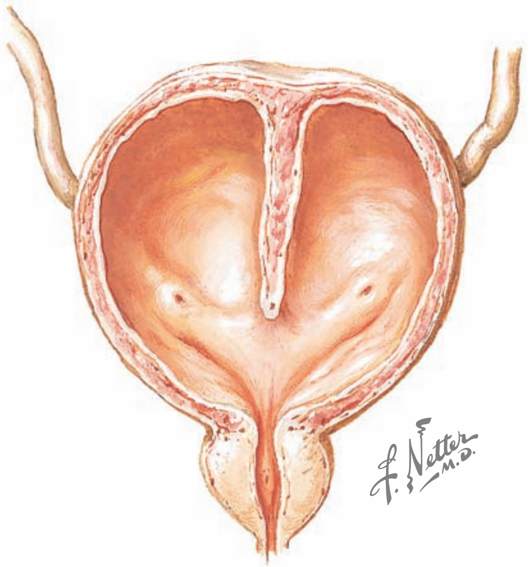
Complete duplication of bladder, urethra, and external genitalia



Partial duplication of bladder, with both halves draining into a single urethra



Complete septation of bladder. The left half does not communicate with the urethra and is thus obstructed, with associated renal abnormalities. The right-sided ureter exhibits vesicoureteral reflux, with associated hydroureteronephrosis.



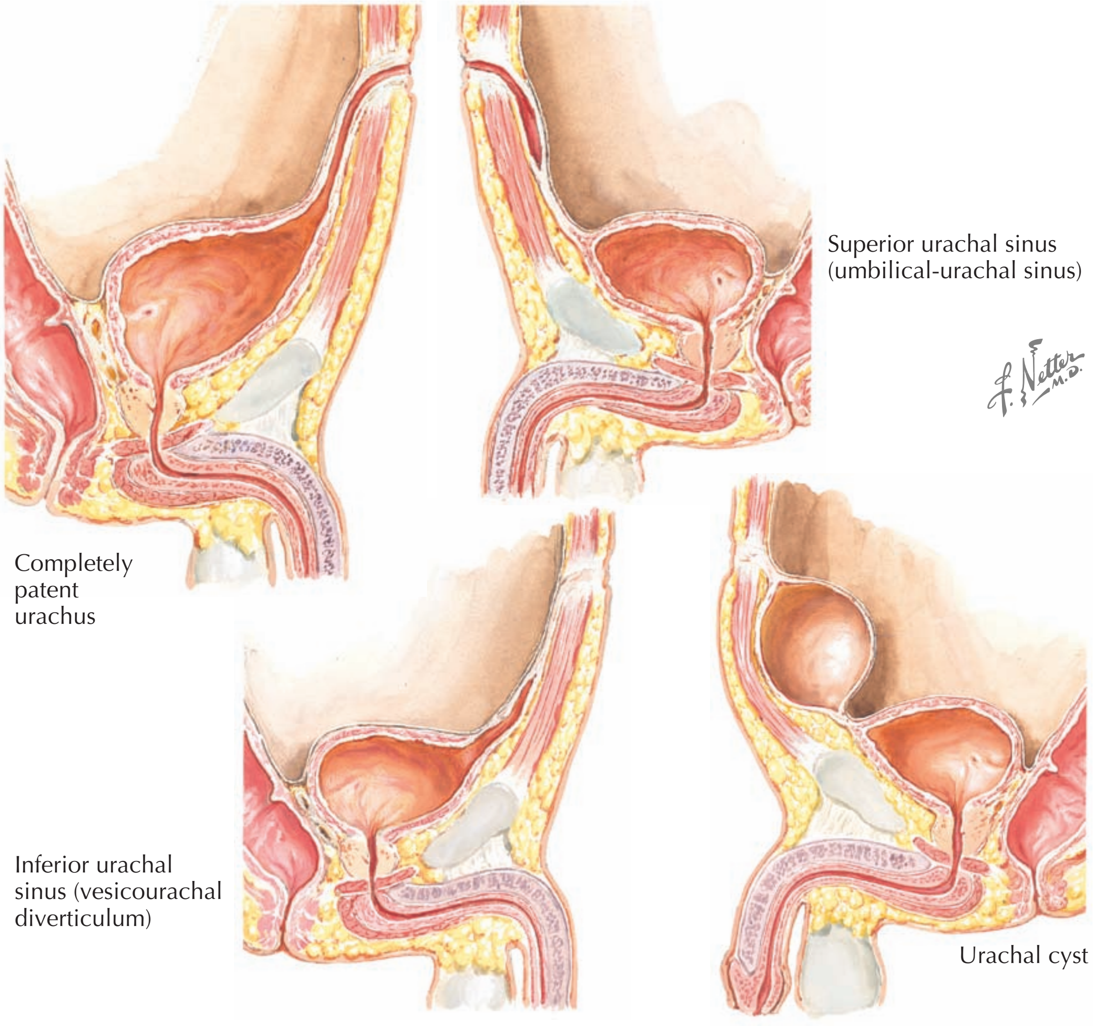
Partial septation of bladder

PRESENTATION AND DIAGNOSIS

The timing of diagnosis depends on the nature and extent of the malformation. If there is external evidence of duplication—such as in the genitals or spine—the patient is likely to undergo comprehensive evaluation early in life, during which the bladder abnormality will be discovered. In contrast, if there is no external evidence of duplication, an evaluation may not be performed unless recurrent febrile urinary tract infections occur (secondary to urine stasis and/or vesicoureteral reflux) or persistent incontinence is noted. In such cases, the bladder anomaly should be noted during imaging with ultrasound, CT, or voiding cystourethrography. Once the diagnosis has been established, further evaluation should include a renal scan to assess kidney function, as well as video-urodynamic studies to examine voiding from each bladder compartment and to determine if vesicoureteral reflux is present.

TREATMENT

The need for surgical intervention depends on the nature and extent of the malformation. If an obstruction is present, it should be excised as soon as possible so as to reduce the risk of further infection and preserve renal function. If incontinence, vesicoureteral reflux, external duplication, and/or other anomalies are present, a more complex intervention will be required, the specifics of which must be tailored to each individual patient.


Completely patent urachus
Superior urachal sinus (umbilical-urachal sinus)
Inferior urachal sinus (vesicourachal diverticulum)
Urachal cyst

ANOMALIES OF THE URACHUS

As described on page 32, the urorectal septum partitions the cloaca into the primitive urogenital sinus and the rectum. The urogenital sinus, which gives rise to the bladder, is initially continuous with the allantois, a tube that extends into the connecting stalk (see Plate 2-4 for an illustration). As the bladder matures and descends into the pelvis, however, the allantois narrows to form a thick, epithelial-lined tube known as the urachus. Normally the urachus regresses into a fibrous cord, known as the median umbilical ligament. For uncertain reasons, however, this normal regression process sometimes fails, resulting in a persistent urachus that is either partially or completely patent. Because many urachal anomalies are undiagnosed, their overall incidence is unknown.

PRESENTATION AND DIAGNOSIS

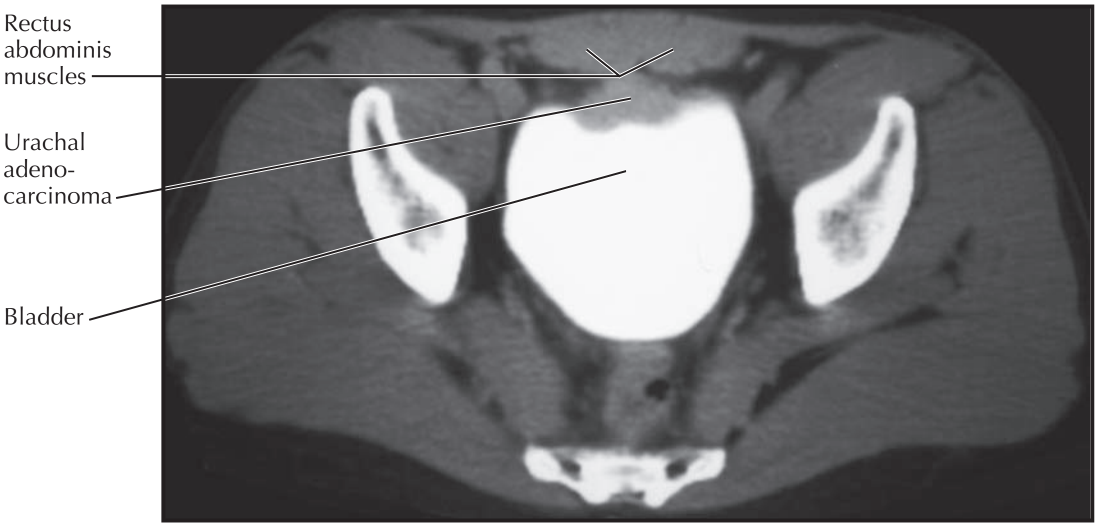
An entirely patent urachus, which permits drainage of urine from the bladder to the umbilicus, accounts for about half of urachal anomalies. It typically presents during the neonatal period as dribbling of fluid from the umbilicus. The fluid leakage may increase in response to bladder contraction during either purposeful voiding or other increases in intraabdominal pressure, such as during crying or straining. Umbilical edema and delayed healing of the umbilical stump may also be noted. The diagnosis can be confirmed with either sonographic evaluation of the bladder or with more invasive studies, such as a retrograde fistulogram or voiding cystourethrogram (VCUG).

A patent area at the distal end of the urachus, which communicates with the umbilicus, is known as a superior urachal sinus (or umbilical-urachal sinus) and accounts for 15% of urachal anomalies. Like a patent urachus, a superior sinus causes umbilical discharge during the neonatal period, although the fluid is not as copious. The diagnosis is best established by performing retrograde sinography.

A patent area in the middle of the urachus, which communicates with neither the umbilicus nor bladder, is known as a urachal cyst and accounts for about 30% of urachal anomalies. A urachal cyst is often not discovered until childhood or adulthood. It may be noted as an incidental finding during laparotomy; as a palpable midline mass; or as a site of infection, usually with *Staphylococcus aureus*, with associated pain and erythema. Either ultrasound or computed tomography can be used to establish the diagnosis.

Finally, a patency in the proximal end of the urachus, which communicates with the apex of the bladder, is known as an inferior sinus (or vesicourachal diverticulum) and accounts for 5% of urachal anomalies. It usually does not cause symptoms because it is has a large opening into the bladder lumen and does not communicate with other structures. In rare instances, however, it may act as a site of calculus formation or lower urinary tract infection. A VCUG, usually performed for some other indication, can establish the diagnosis.

Urachal adenocarcinoma: computed tomography (contrast enhanced)



TREATMENT

A patent urachus or superior sinus should be excised using either an open or laparoscopic technique. It is essential to remove all abnormal urachal tissue because there is a small risk of later malignant transformation. Thus, in addition to the urachus, a cuff of surrounding bladder tissue should be removed as well.

An asymptomatic urachal cyst or inferior sinus can be managed with careful observation since spontaneous resolution is possible. If resolution does not occur, however, or if symptoms emerge, all urachal tissue should be carefully excised.

POSTERIOR URETHRAL VALVES

Posterior urethral valves (PUVs) are abnormal mucosal folds in the distal urethra that arise during fetal development and interfere with the normal outflow of urine. They are the most common cause of congenital urinary tract obstruction, occurring in 1 in 8000 to 1 in 25,000 live births, and are seen only in males. Even if treated early on, the obstruction associated with PUVs frequently causes severe, often permanent urinary tract abnormalities.

The traditional classification system describes two major types of valves, which vary both in morphology and relative frequency. Type I valves, said to account for more than 95% of cases, begin as a mucosal ridge from the seminal colliculus, which extends distally and divides into two flaps that fuse with the walls of the membranous urethra. There is typically incomplete fusion of the flaps with the anterior wall of the urethra, and there is a small opening in the membrane near the posterior wall of the urethra, adjacent to the seminal colliculus. Type III valves, in contrast, are said to account for about 5% of cases and resemble disklike membranes that span the entire circumference of the membranous urethra and contain a small central opening. (Type II valves, extending from the seminal colliculus toward the bladder neck, are no longer thought to be actual valves but rather bladder neck hypertrophy, which accompanies any distal urethral obstruction.) More recent work, however, suggests that in fact all PUVs are membranous, originally resembling type III valves, and that type I valves are actually an artifact of urethral instrumentation, which divides the single membrane into two flaps.

PATHOGENESIS

The male urethra is divided into four portions, the precursors of which become evident early in development. The segments include the prostatic urethra, which extends from the bladder neck to the urogenital diaphragm; the membranous urethra, which traverses the diaphragm; the bulbous urethra, which extends from the urogenital diaphragm to the penoscrotal junction; and the spongy (penile) urethra, which continues through the penile shaft until the urethral meatus.

Between the fourth and sixth weeks of fetal development, the cloaca is divided into the primitive urogenital sinus and the rectum, and the cloacal membrane is likewise divided into the urogenital membrane and rectal membrane. The primitive urogenital sinus has several distinct regions that give rise to the different segments of the lower urinary tract. The dilated cranial region becomes the urinary bladder; the neck just caudal to this region becomes the prostatic and membranous urethra; and the most caudal region, known as the definitive urogenital sinus, becomes the bulbous and spongy urethra.

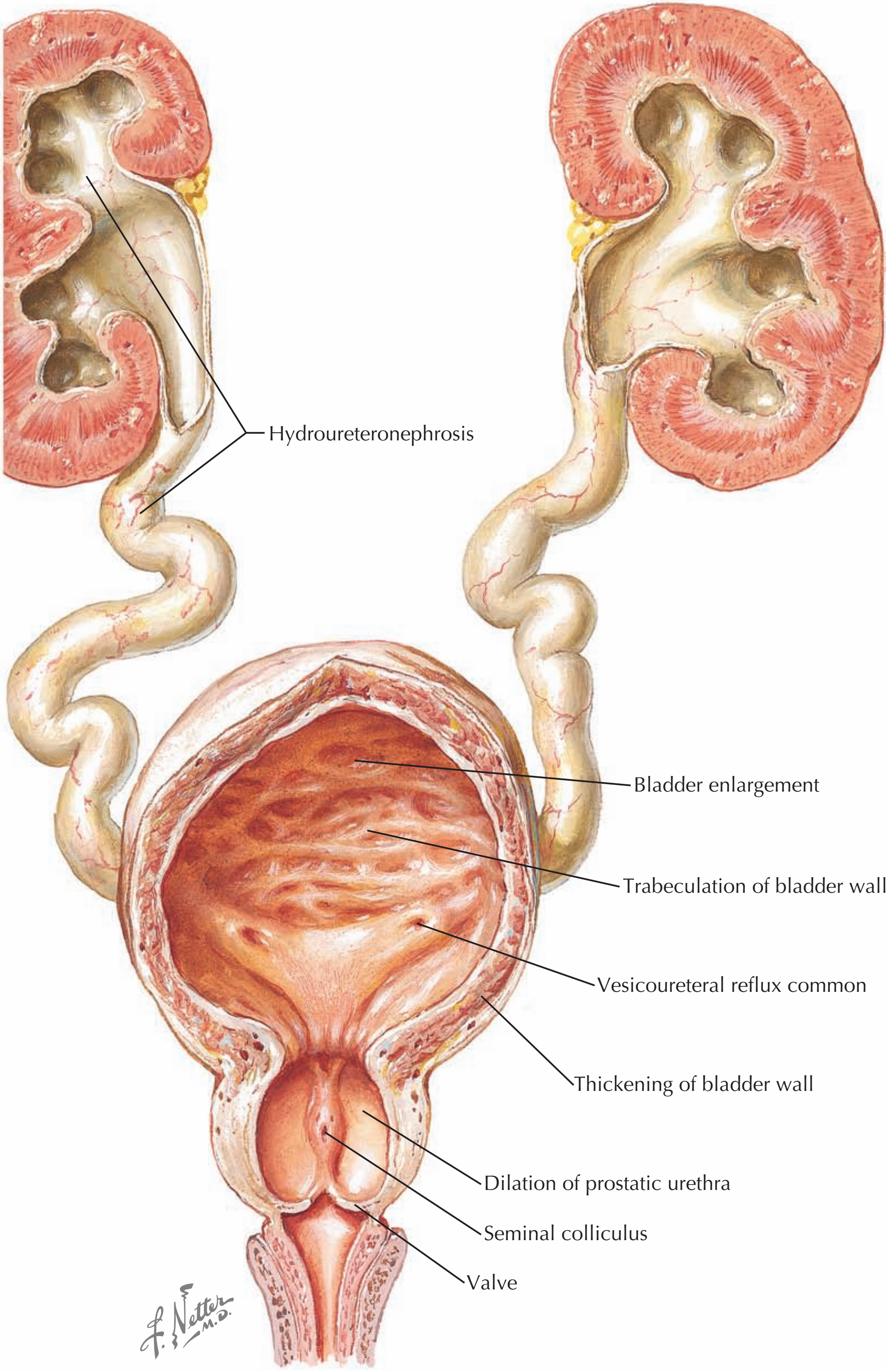
As the urinary tract develops, swellings known as the cloacal folds appear lateral to the cloacal membrane. These folds fuse above the cloaca to form the genital tubercle. As the cloaca is divided, the portions of the cloacal folds lateral to the urogenital membrane become known as the urogenital, or urethral, folds. After the urogenital membrane dissolves, the urethral folds fuse in the midline, encasing the future bulbous and penile urethra.

The developmental abnormality that gives rise to PUVs remains uncertain, at least in part because of the ongoing debate over the precise morphology of this defect. It has been hypothesized, however, that PUVs represent a remnant of an incompletely dissolved urogenital membrane or, alternatively, overdevelopment of a portion of the urethral folds.

PRESENTATION AND DIAGNOSIS

The majority of PUVs are noted on prenatal ultrasonography. Although the valves themselves are too small to be seen, the anatomic sequelae of the chronic outflow obstruction are evident, including dilation of the

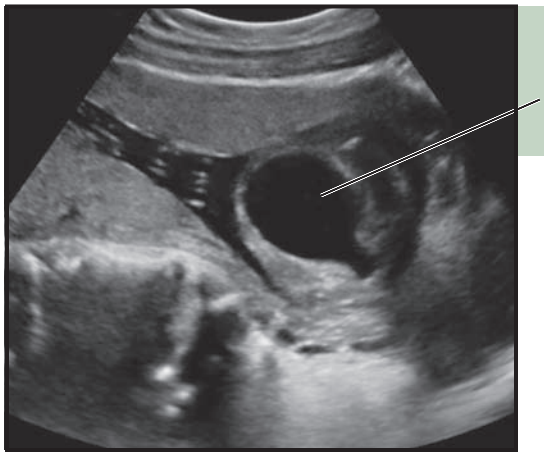
GROSS APPEARANCE OF POSTERIOR URETHRAL VALVES

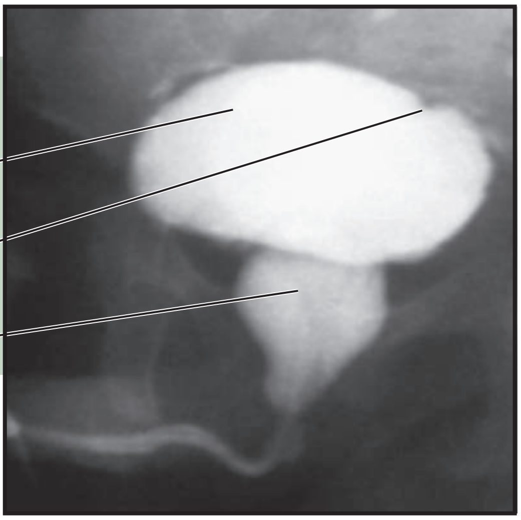

Hydroureteronephrosis
Bladder enlargement
Trabeculation of bladder wall
Vesicoureteral reflux common
Thickening of bladder wall
Dilation of prostatic urethra
Seminal colliculus
Valve
F. Netter M.D.

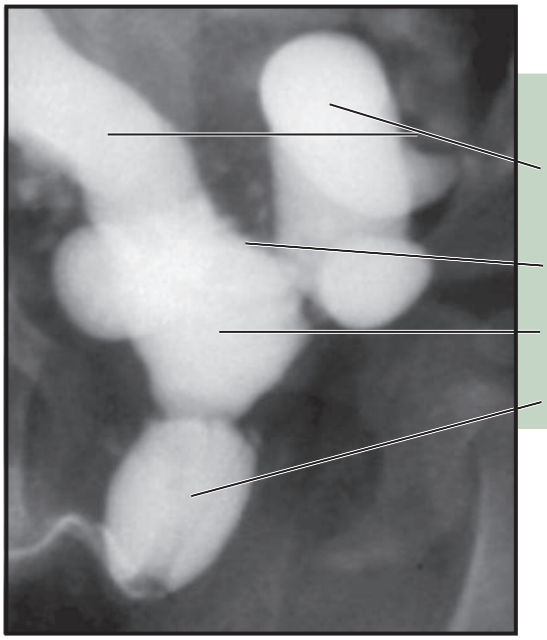
POSTERIOR URETHRAL VALVES

(Continued)

RADIOGRAPHIC FINDINGS OF POSTERIOR URETHRAL VALVES




Voiding cystourethrogram
Dilated bladder
Trabeculation of bladder wall
Dilated prostatic urethra


Voiding cystourethrogram
High-grade, bilateral vesicoureteral reflux, with ureteral dilation
Trabeculation of bladder wall
Contracted bladder (from chronic obstruction)
Dilation of prostatic urethra

prostatic urethra and bladder, thickening of the bladder wall, and bilateral hydroureteronephrosis. The dilated prostatic urethra can be seen caudal to the dilated bladder, a phenomenon known as the "keyhole" sign. The renal parenchyma itself may also appear abnormal, generally manifest as increased echogenicity. If the obstruction is severe, oligohydramnios may be seen. Of note, many of these features may not be prominent if ultrasound is performed before 24 weeks of gestation.

If PUVs are not evident antenatally, their sequelae generally become apparent in the first year of life, with the exact timing depending on the severity of the obstruction.

Patients with the most severe obstructions present at birth with pulmonary hypoplasia and Potter facies owing to oligohydramnios during gestation (see Plate 2-8), as well as enlarged, poorly functional kidneys that may be noted as palpable abdominal masses.

The remaining patients present in the weeks to months after birth with failure to thrive, urinary tract infection, and often a poor urinary stream. On further assessment, these patients are found to have renal insufficiency, which results not only from obstruction-induced damage to the renal tubules, but also from renal dysplasia secondary to a developmental obstruction to urine outflow.

The definitive diagnostic test in the infant is a voiding cystourethrogram (VCUG), which reveals dilation of the bladder and prostatic urethra. The valves themselves may be visible as urethral filling defects. The bladder wall may appear trabeculated and contain diverticula, both of which reflect chronic obstruction (see Plate 6-2). A variable degree of vesicoureteral reflux may also be seen because even normally formed ureterovesical junctions may be unable to tolerate the high pressure resulting from the outlet obstruction. In addition to the VCUG, a renal scan may also be performed to assess the remaining level of renal function and measure the severity of the obstruction.

TREATMENT

The first goal of treatment is urinary drainage. Although prenatal interventions have been attempted in an effort to limit damage to the developing kidneys, this is not a common practice, and thus most patients are treated immediately after birth. In most cases, draining the bladder can be accomplished simply by placing a urethral catheter. In the acute period, patients may require a host of additional interventions to address the pulmonary hypoplasia that can result from oligohydramnios, as well as the fluid and electrolyte abnormalities that can occur secondary to renal insufficiency.

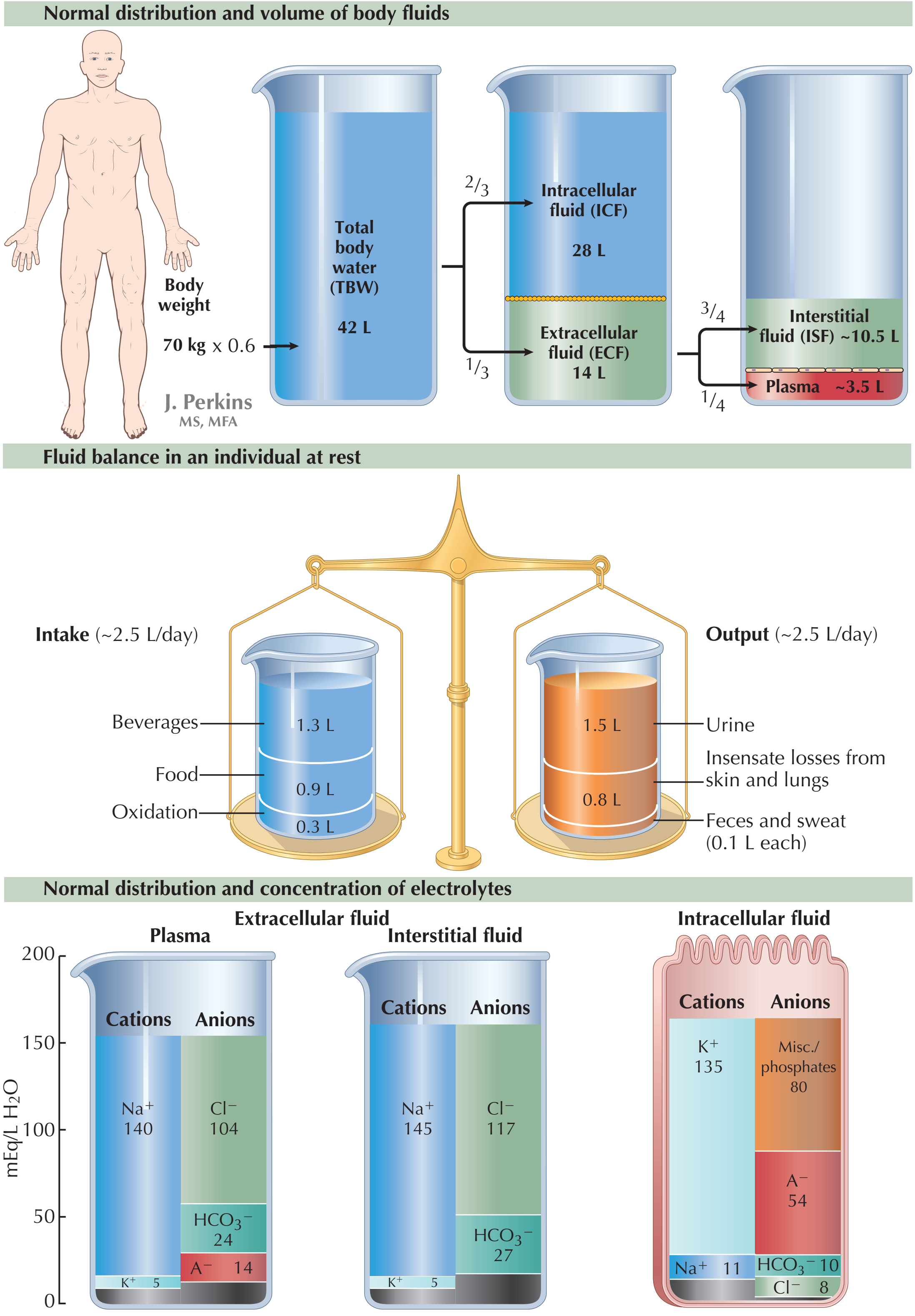
Once bladder drainage has been established, the patient can be monitored for several weeks. After this period, the treatment of choice for full-term, normal-sized infants is cystoscopic valve ablation using a laser, cold knife, hook, or other device. It is important to permit urination immediately after the ablation to prevent stricture formation. In a premature or low-birth-weight neonate with a small caliber urethra that would not permit endoscopic ablation, a cutaneous vesicostomy may be performed as a temporizing measure. Once the infant is older and the urethra is large enough to accommodate a pediatric cystoscope, delayed valve ablation and eventual reversal of the vesicostomy can be performed.

The long-term clinical syndrome that results from PUVs is known as the "valve-bladder syndrome." Affected patients have large bladder volumes and subsequent overflow incontinence, which occur because bladder compliance and sensation decrease in response to longstanding obstruction. The large bladder volumes perpetuate obstructive injury to the kidneys. The injured kidneys, in turn, worsen the overfilling problem because their damaged collecting ducts become unable to appropriately concentrate urine. Some of these changes may be reversible if bladder pressure is regularly reduced, as with clean intermittent catheterization.

SECTION 3

PHYSIOLOGY

OVERVIEW OF FLUIDS AND ELECTROLYTES


Normal distribution and volume of body fluids
Body weight
70 kg x 0.6
Total body water (TBW)
42 L
2/3
Intracellular fluid (ICF)
28 L
1/3
Extracellular fluid (ECF)
14 L
3/4
Interstitial fluid (ISF) ~10.5 L
1/4
Plasma ~3.5 L
J. Perkins
MS, MFA
Fluid balance in an individual at rest
Intake (~2.5 L/day)
Beverages
1.3 L
Food
0.9 L
Oxidation
0.3 L
Output (~2.5 L/day)
1.5 L
Urine
Insensate losses from skin and lungs
0.8 L
Feces and sweat (0.1 L each)
Normal distribution and concentration of electrolytes
Extracellular fluid
Plasma
Interstitial fluid
Intracellular fluid
mEq/L H2O
200
150
100
50
0
Cations
Anions
Na+ 140
Cl− 104
HCO3− 24
A− 14
K+ 5
Na+ 145
Cl− 117
HCO3− 27
K+ 5
K+ 135
Misc./ phosphates 80
A− 54
Na+ 11
HCO3− 10
Cl− 8

BASIC FUNCTIONS AND HOMEOSTASIS

Blood enters the kidneys in a series of branching vessels that give rise to afferent arterioles. Each afferent arteriole leads to a tuft of glomerular capillaries. Plasma and small, non–protein bound solutes are filtered across the walls of the glomerular capillaries into Bowman's space, the initial portion of the nephron. From there, the filtrate is conveyed through the remaining segments of the nephron—which include the proximal tubule, thin limb, distal tubule, and collecting duct—before being excreted in the final urine.

In the various segments of the renal tubules, there is extensive exchange of material with the surrounding capillaries. Such exchange is known as "reabsorption" if materials are transferred from the tubular lumen to the capillaries and/or interstitium, and as "secretion" if they are transferred in the opposite direction.

By continuously adjusting the contents of blood, the kidneys make critical contributions to the maintenance of fluid and salt homeostasis, as well as to the excretion of unwanted chemicals and waste products. In addition, the kidneys contribute to the regulation of arterial pressure, acid-base status, erythropoiesis, and vitamin D synthesis.

MECHANISMS OF HOMEOSTASIS

To maintain homeostasis, the kidneys must adjust their retention or excretion of fluid and filtered solutes so that, in cooperation with other excretory organs (lungs, skin, bowel), overall output equals intake.

Water, for example, accounts for approximately 60% of total body weight. Approximately two thirds of this volume is intracellular, whereas the remaining third is extracellular. Each day, the average individual consumes approximately 2000 to 2500 mL of water, while carbohydrate oxidation produces another 200 to 300 mL of water. At baseline, these input volumes must be offset by an equal amount of output. On an average day, the kidneys excrete approximately 1500 mL of water, while sweat and feces each contain approximately 100 mL of water. The remaining water is insensibly lost through the skin and lungs.

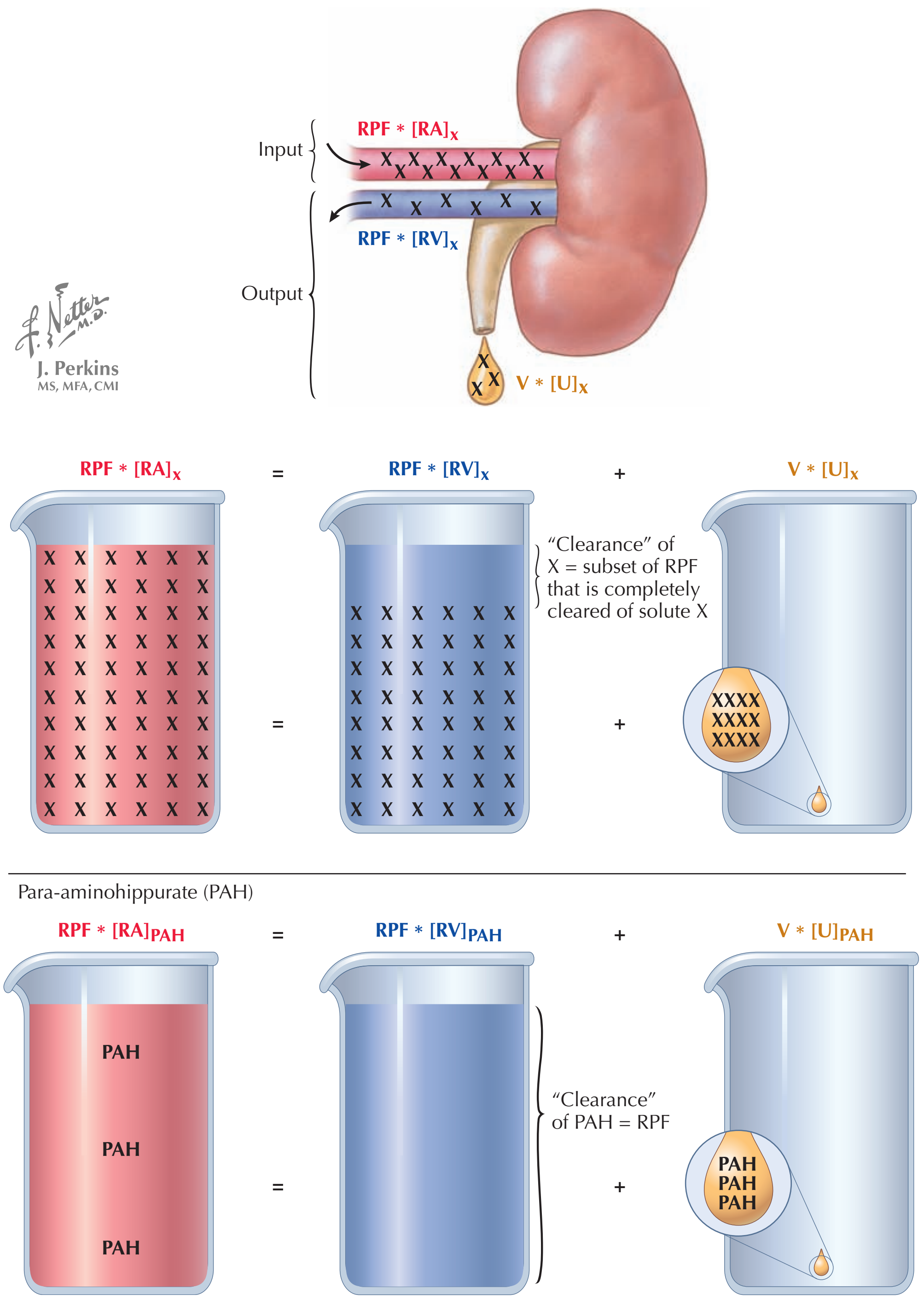
During significant physical exertion, a greater amount of water is lost as sweat and insensible losses. As a result, the relative amount of fluid excreted as urine decreases. Likewise, a person who is severely dehydrated needs to produce far less urine than a person who consumes a large volume of water. A reduction in urine volume could be effected by reducing the rate of plasma filtration from the glomerular capillaries into nephrons; however, this would be an impractical response because the kidneys would consequently be unable to excrete other unwanted substances. Instead, the kidneys continue to filter a large amount of plasma, but they increase the rate of fluid reabsorption from the tubules so that the final urine volume remains low.

The same basic mechanism applies to solutes, such as potassium, calcium, and other salts, the concentrations of which are maintained in very narrow ranges in the extracellular and intracellular spaces. The kidneys filter these solutes at a largely constant rate, but they alter their rate of excretion based on input from homeostatic sensor mechanisms. Solute excretion can be adjusted by altering the rate of either reabsorption or secretion. Many substances are reabsorbed or secreted using active, transcellular mechanisms that can be very finely tuned.

The signals that modulate these processes differ depending on the substance in question. For example, aldosterone is released in response to elevated extracellular potassium levels and promotes increased potassium secretion (see Plate 3-10). In contrast, parathyroid hormone (PTH) is released in response to decreased calcium levels and promotes a net increase in calcium reabsorption (see Plate 3-11). The details of these homeostatic mechanisms, as well as some of the complications that occur when they are disturbed, are discussed in detail later in this section.

CLEARANCE AND RENAL PLASMA FLOW

CLEARANCE AND ESTIMATION OF RENAL PLASMA FLOW



CLEARANCE

Solutes that cannot be metabolized, such as sodium and potassium, enter the kidneys in arterial blood and then leave in venous blood and urine. At a steady state, such solutes are not retained within the kidneys. Thus the rate at which a non-metabolized solute *x* enters the kidneys is equal to the rate at which it leaves, as expressed in the following equation:

$$\mathrm{RPF} \times [\mathrm{RA}]_x = (\mathrm{RPF} \times [\mathrm{RV}]_x) + (\dot{V} \times [\mathrm{U}]_x)$$

RPF = renal plasma flow
$[\mathrm{RA}]_x$ = concentration of *x* in renal arterial blood
$[\mathrm{RV}]_x$ = concentration of *x* in renal venous blood
$\dot{V}$ = rate of urine production
$[\mathrm{U}]_x$ = concentration of *x* in urine

(Because RPF >>> $\dot{V}$, both renal arterial and renal venous flow can be considered equal to RPF, even though the former is slightly greater than the latter.)

By rearrangement,

$$\mathrm{RPF}([\mathrm{RA}]_x - [\mathrm{RV}]_x) = \dot{V} \times [\mathrm{U}]_x$$

With this formulation, it is evident that the rate at which *x* is extracted from renal blood is equal to the rate at which it is excreted in urine.

The "clearance" of substance x, also known as C(x), is equal to the hypothetical subset of RPF from which *x* is completely removed ("cleared") as it passes through the kidneys. For this subset, $[\mathrm{RV}]_x$ is equal to zero. Thus by substituting C(x) for RPF in the above equation:

$$\mathrm{C}(x) \times [\mathrm{RA}]_x = \dot{V} \times [\mathrm{U}]_x$$

Since $[\mathrm{RA}]_x$ is always equal to the systemic plasma concentration of *x* ($[\mathrm{P}]_x$), one can make further substitutions and rearrange to solve for C(x):

$$\mathrm{C}(x) = \frac{\dot{V} \times [\mathrm{U}]_x}{[\mathrm{P}]_x}$$

It is often useful to compare clearances of different substances because these values offer basic information about how they are handled in the nephrons. Specifically, substances that undergo net secretion into the renal tubules will have higher clearance values than those substances that undergo only filtration, whereas those that undergo net reabsorption will have lower clearance values (see Plate 3-6).

RENAL PLASMA FLOW

The clearance principle can be used to determine the rate of renal plasma flow. As stated above,

$$\mathrm{RPF}([\mathrm{RA}]_x - [\mathrm{RV}]_x) = \dot{V} \times [\mathrm{U}]_x$$

If the entire RPF is "cleared" of *x*, meaning all of the *x* that enters the kidneys is excreted in urine, $[\mathrm{RV}]_x$ equals zero in the above equation, such that:

$$\mathrm{RPF}([\mathrm{RA}]_x) = \dot{V} \times [\mathrm{U}]_x$$

By simple substitution and rearrangement,

$$\mathrm{RPF} = \frac{\dot{V} \times [\mathrm{U}]_x}{[\mathrm{P}]_x}$$

$$\mathrm{RPF} = \mathrm{C}(x)$$

Nearly all of the para-aminohippurate (PAH) that enters the kidneys is transferred from blood to urine through a combination of filtration and secretion. Thus $[\mathrm{RV}]_{\mathrm{PAH}}$ is equal to almost zero under normal circumstances. As a result, C(PAH) approximates RPF. A small amount of PAH does reach the renal vein, however, because of the tiny fraction of blood that is shunted past the filtration and secretion apparatus. As a result, C(PAH) slightly underestimates RPF, with the discrepancy growing larger in conditions that increase the shunted volume.

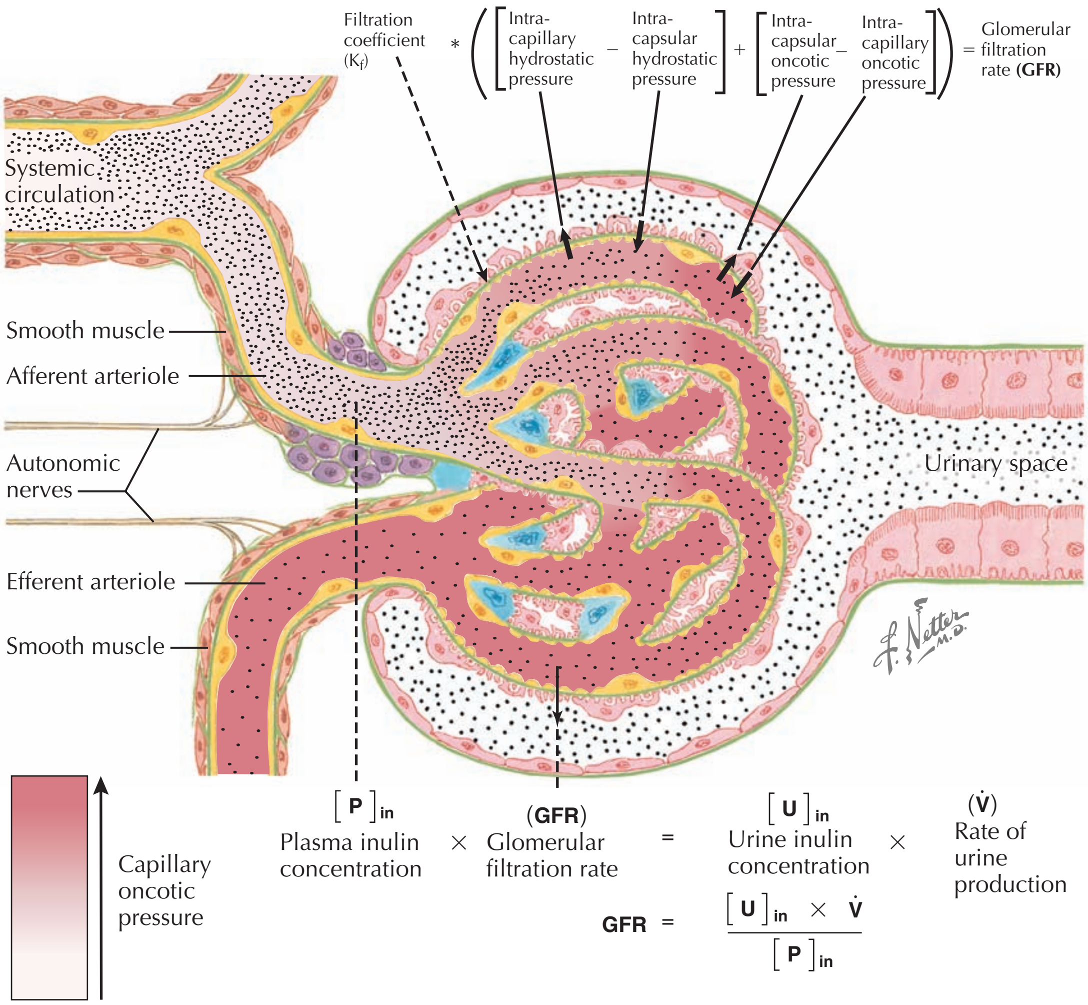
Renal Blood Flow. Once RPF is known, a simple equation permits conversion to renal blood flow (RBF):

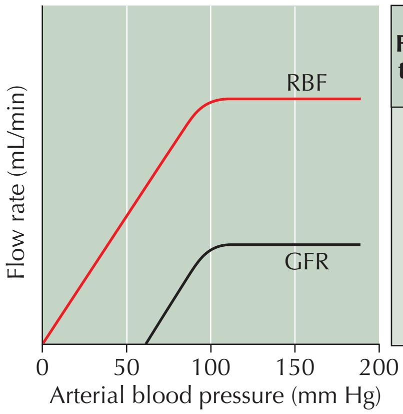
$$\mathrm{RPF} = \mathrm{RBF} \times (1\text{-hematocrit})$$

RBF is typically equal to about 20% to 25% of the total cardiac output, or about 1 to 1.5 L/min. Since the kidneys together account for less than 0.5% of total body weight, they are very richly perfused compared with other organs. Such perfusion, which far exceeds their metabolic needs, permits extensive filtration and fine-tuning of plasma contents. The overwhelming majority of blood flow is directed toward the cortex, which contains the glomerular capillaries.

The kidneys have numerous autoregulation mechanisms that maintain renal blood flow nearly constant over a wide range of systemic arterial pressures. These mechanisms operate by adjusting the renal vascular resistance, primarily in the cortical radiate (interlobular) arteries, afferent arterioles, efferent arterioles, and peritubular capillaries. These vessels are under the control of numerous hormones and sympathetic input, as described on Plate 3-18.

GLOMERULAR FILTRATION RATE


Filtration coefficient (K_f)
*
Intra-capillary hydrostatic pressure
−
Intra-capsular hydrostatic pressure
+
Intra-capsular oncotic pressure
−
Intra-capillary oncotic pressure
= Glomerular filtration rate **(GFR)**
Systemic circulation
Smooth muscle
Afferent arteriole
Autonomic nerves
Efferent arteriole
Smooth muscle
Urinary space
Capillary oncotic pressure
$[P]_{in}$ Plasma inulin concentration
×
(GFR) Glomerular filtration rate
=
$[U]_{in}$ Urine inulin concentration
×
($\dot{V}$) Rate of urine production
GFR = $\frac{[U]_{in} \times \dot{V}}{[P]_{in}}$
F. Netter M.D.



Factors that constrict the afferent arteriole	Factors that constrict the efferent arteriole	Factors that dilate the afferent arteriole
Angiotensin II (mildly) Norepinephrine Endothelin	Angiotensin II Norepinephrine Endothelin Atrial natriuretic peptide (ANP)	Atrial natriuretic peptide (ANP) Prostaglandins Nitric oxide Dopamine

GLOMERULAR FILTRATION RATE

GLOMERULAR FORCES THAT DETERMINE FILTRATION RATE

Blood that enters the glomerular capillaries is filtered into Bowman's space, the first region of the nephron. The glomerular filtration rate (GFR) is equal to the volume of plasma filtered through the capillary walls per unit of time, and it depends on the pressure differential (both hydrostatic and oncotic) between the glomerular capillaries and Bowman's space. Hydrostatic pressure in the glomerular capillaries, as well as oncotic pressure in Bowman's space, favor filtration. In contrast, hydrostatic pressure in Bowman's space, as well as oncotic pressure in the glomerular capillaries, oppose filtration.

These relationships can be expressed using the following equation:

$$GFR = Kf[(P_{gc} - P_{bs}) + (\pi_{bs} - \pi_{gc})]$$

Kf = filtration coefficient
P = hydrostatic pressure
p = oncotic pressure
gc = glomerular capillaries
bs = Bowman space

The filtration coefficient Kf depends on characteristics of the glomerular capillary walls, such as total surface area and permeability. Thus processes that promote loss of glomeruli, such as glomerulosclerosis, or thickening of the capillary walls, such as diabetes mellitus, lower the GFR.

P_{gc} depends on systemic arterial pressure and the resistance in the afferent and efferent arterioles. It is constant along the length of the glomerular capillaries.

π_{gc} depends on plasma oncotic pressure, and it increases as fluid approaches the efferent arteriole because removal of plasma fluid concentrates nonfilterable proteins. As π_{gc} increases, the forces favoring and opposing filtration eventually become equal. This point is known as filtration equilibrium.

Both P_{gc} and π_{gc} change in response to constriction or dilation of the afferent and efferent arterioles. For example, constriction of the efferent arteriole increases P_{gc} but reduces renal plasma flow, which slows the rate at which blood passes through the glomerular capillaries. Because plasma therefore spends more time in contact with the filtration surface, π_{gc} rises more rapidly along the length of the capillaries. Thus the GFR remains largely constant because the changing hydrostatic and oncotic forces are balanced. In contrast, constriction of the afferent arteriole decreases P_{gc} and causes an earlier rise in π_{gc}, decreasing the GFR. Finally, dilation of the afferent arteriole increases P_{gc} and causes a later rise in π_{gc}, increasing the GFR.

Several agents alter tone in the afferent and efferent vessels. The most important include angiotensin II (AII), which preferentially constricts the efferent arteriole, maintaining the GFR constant; norepinephrine (i.e., sympathetic input), which constricts both afferent and efferent arterioles, reducing the GFR; atrial natriuretic peptide (ANP), which dilates the afferent arteriole and constricts the efferent arteriole, increasing the GFR; and prostaglandins, which dilate the afferent arteriole, increasing the GFR.

Under normal circumstances, the pressures in Bowman's space are less variable and less important than those in the glomerular capillaries. P_{bs} depends on pressures throughout the urinary collecting system and may be increased in the presence of a urine outflow obstruction. Normally, π_{bs} is negligible.

GLOMERULAR FILTRATION RATE *(Continued)*

CALCULATION OF GFR

In clinical practice, it is not possible to measure hydrostatic or oncotic pressure in the glomerular capillaries or in Bowman's space. Instead, the GFR can be determined based on the rate at which specific molecular markers enter the urine. For all solutes,

filtration rate + secretion rate − reabsorption rate = excretion rate

For a solute *x* that is freely filtered at the glomerulus, then neither reabsorbed nor secreted:

filtration rate = excretion rate

$$[P]_x \times GFR = \dot{V} \times [U]_x$$

$[P]_x$ = concentration of x in plasma
GFR = glomerular filtration rate
$[U]_x$ = concentration of x in urine
$\dot{V}$ = rate of urine production

Rearranging, and recalling the clearance formula introduced previously, it is evident that:

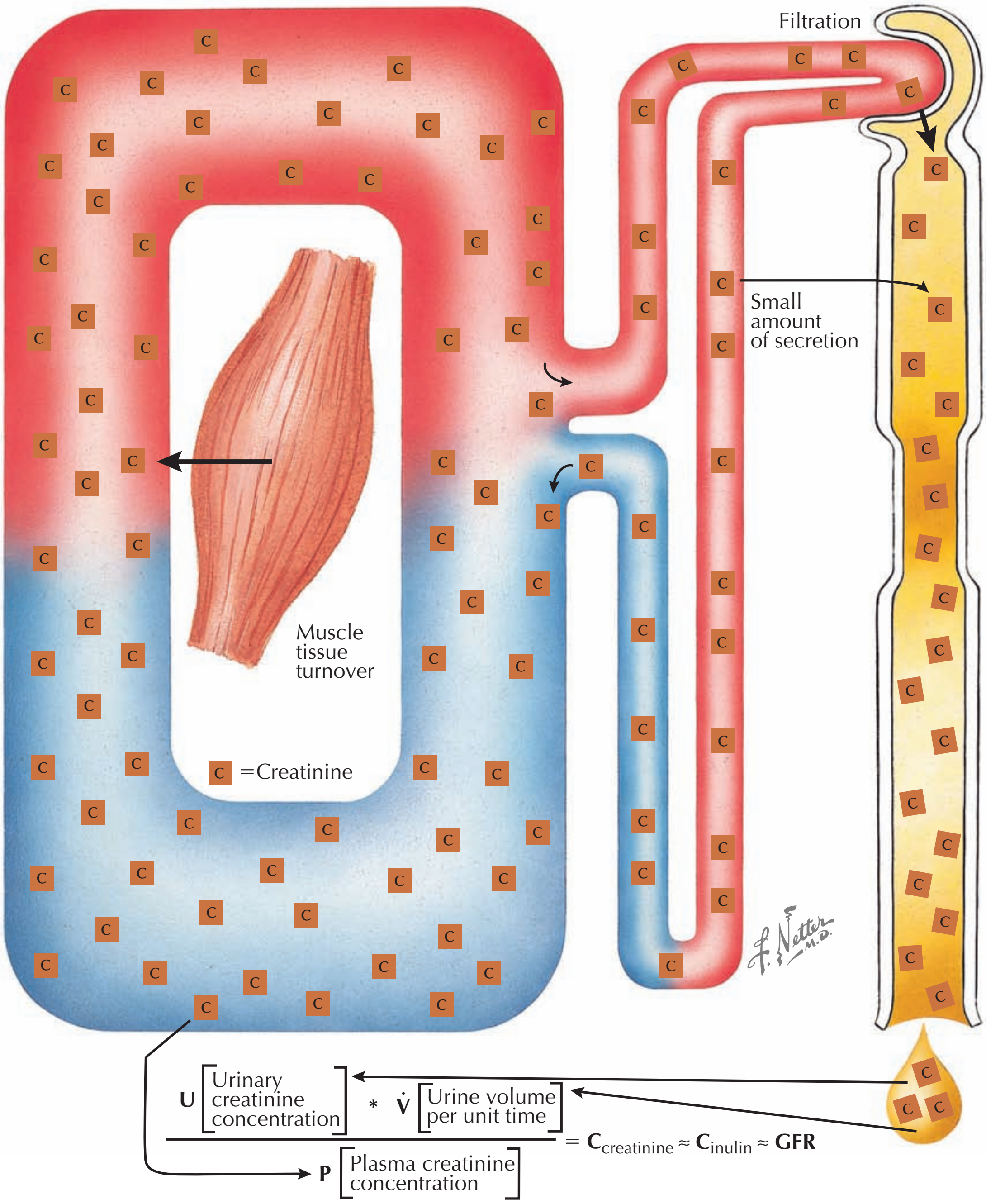
$$C(x) = GFR$$

Thus for a solute *x* that is freely filtered and then neither reabsorbed nor secreted, the volume of plasma cleared of *x* per unit of time is equal to the volume of plasma filtered per unit of time.

Inulin, a fructose polysaccharide, is an example of a substance that is filtered but neither reabsorbed nor secreted. Therefore, calculating its clearance provides a reasonable approximation of the GFR.

In the clinical setting, however, it is often impractical to measure the clearance of inulin, since it is an exogenous substance that must be administered until steady-state concentrations are reached. Moreover, there is a risk of anaphylactoid reactions. Instead, creatinine clearance (Ccr) is calculated, since creatinine is an endogenous chemical that is filtered at the glomerulus, undergoes little secretion, and is usually at a steady-state concentration in plasma. It originates from creatine and phosphocreatine in skeletal muscle, which are normally metabolized at a relatively constant rate. Creatinine clearance provides a close approximation of the GFR, but it tends to overestimate by up to 10% to 20%, owing to the small amount of creatinine secretion. This error increases when the GFR is low, since secretion then accounts for a relatively greater fraction of creatinine's overall clearance.

CALCULATION OF GLOMERULAR FILTRATION RATE
Creatinine clearance


Filtration
Small amount of secretion
Muscle tissue turnover
C =Creatinine
C
U Urinary creatinine concentration
* $\dot{V}$ Urine volume per unit time
P Plasma creatinine concentration
= $C_{creatinine} \approx C_{inulin} \approx$ GFR

Equations for estimating creatinine clearance and GFR

Cockcroft-Gault formula

$$eC_{cr} = \frac{(140-\text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \textit{ if female}]}{72 \times \text{Serum creatinine (in mg/dL)}}$$

Modification of diet in renal disease (MDRD) formula

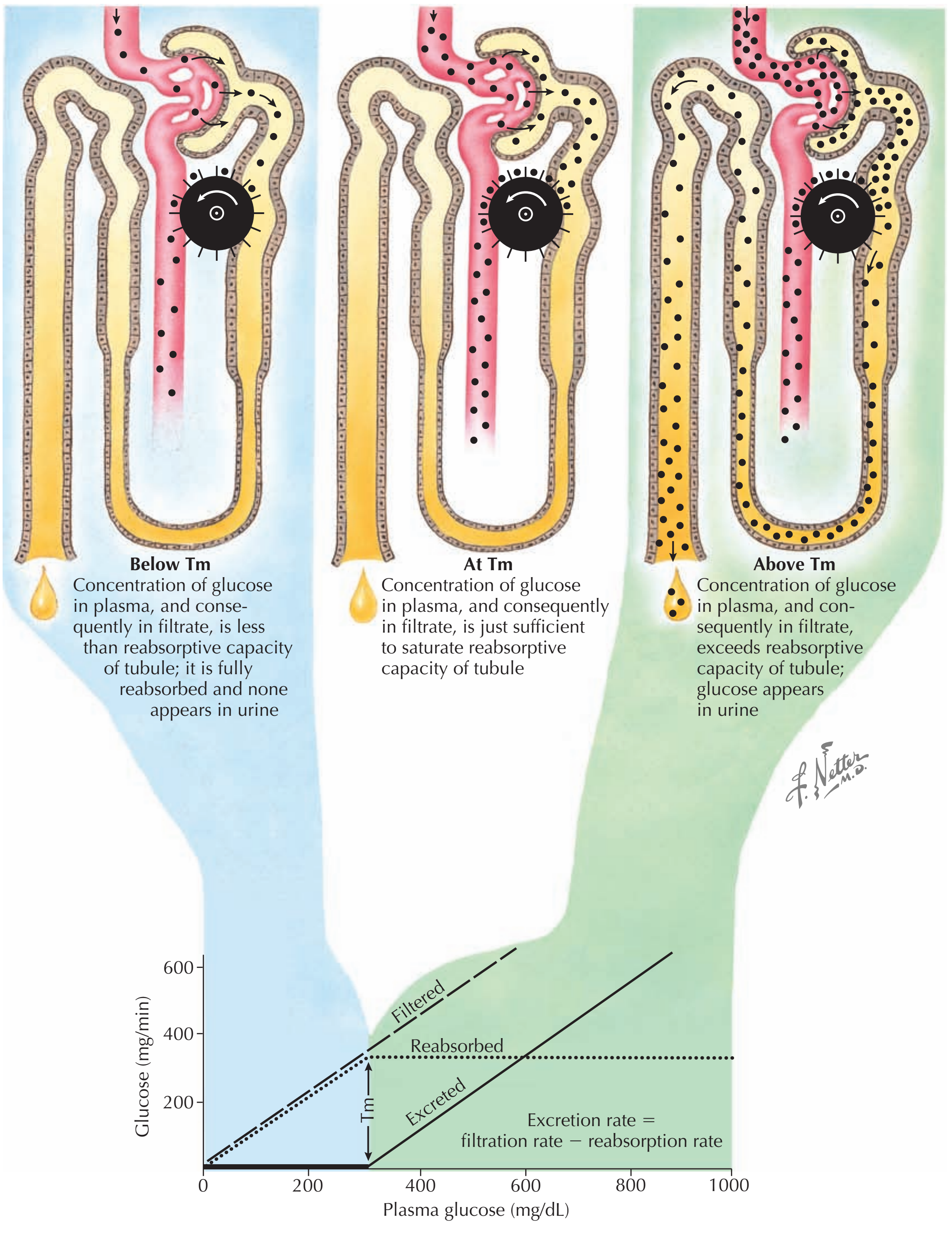
$$eGFR = 186 \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \textit{ if black}] \times [0.742 \textit{ if female}]$$

To obtain a precise value for creatinine clearance, and thus a close estimate of the GFR, one could collect a 24-hour urine sample and solve for Ccr as $\dot{V}*[U]_{Cr}/[P]_{Cr}$. Because of the inconvenience of 24-hour collections, however, most clinicians instead rely on regression equations that estimate Ccr based on $[P]_{Cr}$. These estimates use age, sex, weight, and race as corrective factors, since an individual's normal creatinine concentration depends on his or her muscle mass. Examples include the Cockcroft-Gault and MDRD formulas.

The average GFR in a normal individual is 120 to 130 mL/minute. Because the relationship between GFR and $[P]_{Cr}$ is inverse and exponential, a doubling of $[P]_{Cr}$ indicates the GFR has declined by half. A decline in the GFR to abnormally low values is known as renal insufficiency; if it occurs over a short time period, it is known as acute kidney injury (or acute renal failure, see Plate 4-1); if it is sustained, it is known as chronic kidney disease (or chronic renal failure, see Plate 4-66).

By calculating GFR/RPF, one can obtain the filtration fraction, defined as the fraction of plasma reaching the glomerular capillaries that is filtered into Bowman's space. Normal values for filtration fraction are around 20%.

TUBULAR REABSORPTION AND SATURATION KINETICS


Below Tm
Concentration of glucose in plasma, and consequently in filtrate, is less than reabsorptive capacity of tubule; it is fully reabsorbed and none appears in urine

At Tm
Concentration of glucose in plasma, and consequently in filtrate, is just sufficient to saturate reabsorptive capacity of tubule

Above Tm
Concentration of glucose in plasma, and consequently in filtrate, exceeds reabsorptive capacity of tubule; glucose appears in urine

Excretion rate = filtration rate − reabsorption rate

SECRETION AND REABSORPTION

As filtered fluid passes through the nephron, solutes may undergo reabsorption from the tubular fluid to the interstitium and capillaries, as well as secretion in the opposite direction. Thus,

filtration rate + secretion rate − reabsorption rate = excretion rate

For solute *x*, one can express this process using the following equation:

$$([P]_x \times GFR) + SR_x - RR_x = [U]_x \times \dot{V}$$

$[U]_x$ = concentration of x in urine
$\dot{V}$= rate of urine production
$[P]_x$ = concentration of x in plasma
GFR = glomerular filtration rate
SR = secretion rate
RR = reabsorption rate

The specific handling of individual solutes will be discussed later in the pages that follow. In general, however, secretion and reabsorption of solutes may occur along transcellular (through cells) or paracellular (between cells) pathways. Unlike filtration, which is largely nonselective, secretion and reabsorption are selective processes that can be finely adjusted to modulate the final excretion rate of individual solutes.

TRANSCELLULAR AND PARACELLULAR PATHWAYS

Transcellular pathways depend on the presence of membrane proteins, such as transporters and ion channels, which allow solutes to enter and exit cells. Paracellular pathways, in contrast, depend on diffusive or convective forces, which carry solutes between cells. Differences in these transport methods have several important consequences.

First, transcellular routes can be finely modulated by altering the presence or function of the involved membrane proteins. Paracellular routes, in contrast, can in general only be coarsely modulated by adjusting the forces for diffusion or convection. Thus the homeostatic feedback mechanisms providing hormonal input to the kidneys primarily affect transcellular pathways.

Second, transcellular routes can become saturated, reflecting the limited number and capacity of membrane proteins, whereas paracellular routes generally cannot. In some cases, it is desirable to induce saturation for therapeutic purposes. For example, probenecid and penicillin are both secreted using the same transporters in the proximal tubule. Deliberate administration of high-dose probenecid will saturate those transporters, blocking secretion of penicillin and thereby prolonging its half-life. In other cases, saturation may be a sign of a disease process. Under normal conditions, for example, glucose readily enters the tubular filtrate but is completely reabsorbed, such that none appears in the urine. In diabetes mellitus, however, plasma glucose levels can become so high that the filtered load saturates the reabsorption apparatus, causing glucose to appear in the urine.

Based on the equation given above, the rate at which glucose is excreted in urine can be expressed as follows:

$$[U]_{Glucose} \times \dot{V} = ([P]_{Glucose} \times GFR) + SR_{Glucose} - RR_{Glucose}$$

Because glucose is not secreted, $SR_{Glucose}$ is equal to zero. In normal individuals, the reabsorption rate ($RR_{Glucose}$) is equal to the filtration rate ($[P]_{Glucose} \times GFR$), such that $[U]_{Glucose}$ is zero. Once the reabsorption pathways are saturated and $RR_{Glucose}$ reaches a

SECRETION AND REABSORPTION *(Continued)*

tubular maximum (Tm), however, the excreted load will vary in proportion to the filtered load. Such saturation tends to occur once serum glucose concentrations exceed 300 mg/dL.

QUANTIFYING REABSORPTION AND SECRETION

One means of assessing the secretion or reabsorption profile of a particular solute is to examine its changing concentration along the length of the nephron. As filtrate enters Bowman's space, each solute *x* has an initial tubular concentration, $[T]_x$. For substances that freely cross the glomerular capillaries, the initial $[T]_x$ equals the plasma concentration, $[P]_x$. As filtrate progresses through the nephron, however, $[T]_x/[P]_x$ changes. If it exceeds one, the tubular concentration of *x* has increased, suggesting either secretion of *x* or reabsorption of water. If [T]x/[P]x remains equal to one, there has been either no secretion or reabsorption, or there has been equal reabsorption of *x* and water. Thus in all instances one must control for the reabsorption of water. Because inulin is, as previously described, a compound that is filtered but neither secreted nor reabsorbed, one can use its concentration to infer water reabsorption. If $[T]_{inulin}$ doubles relative to $[P]_{inulin}$, then half of the water has been reabsorbed.

In Bowman's space, $([T]_x/[P]_x) = ([T]_{inulin}/[P]_{inulin}) = 1$. If, at some later point in the nephron, $([T]_x/[P]_x)/([T]_{inulin}/[P]_{inulin}) = ½$, it suggests that half of the water, as well as half of solute *x*, have been reabsorbed. If none of solute *x* had been reabsorbed, the quotient would be equal to 1, since removing half of the filtered water would have doubled the tubular concentration of x relative to plasma, just as for inulin.

One can assess the overall reabsorption and secretion pattern of any given solute by examining $([U]_x/[P]_x) / ([U]_{inulin}/[P]_{inulin})$, a ratio known as the fractional excretion (FE) of *x*. For those substances that are not freely filtered at the glomerulus, such as ions partially bound to plasma proteins, the plasma concentration should be multiplied by the free fraction.

If FE(x) equals 0.01, then 99% of the filtered *x* has been reabsorbed. In contrast, if FE(x) is greater than 1, then there has been net secretion of *x*. FE(x) can also be viewed as a "clearance ratio," which may be easier to conceptualize:

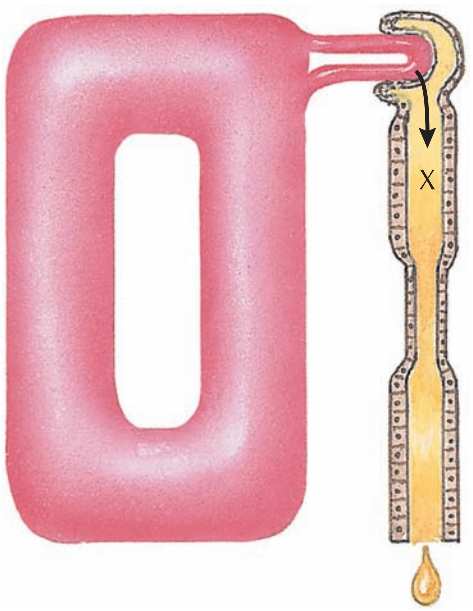
$$FE(x) = \frac{\left(\frac{[U]_x}{[P]_x}\right)}{\left(\frac{[U]_{inulin}}{[P]_{inulin}}\right)} = \frac{\left([U]_x \times \frac{\dot{V}}{[P]_x}\right)}{\left([U]_{inulin} \times \frac{\dot{V}}{[P]_{inulin}}\right)}$$

$$= \frac{\text{clearance of x}}{\text{clearance of inulin}} = \frac{C(x)}{GFR}$$

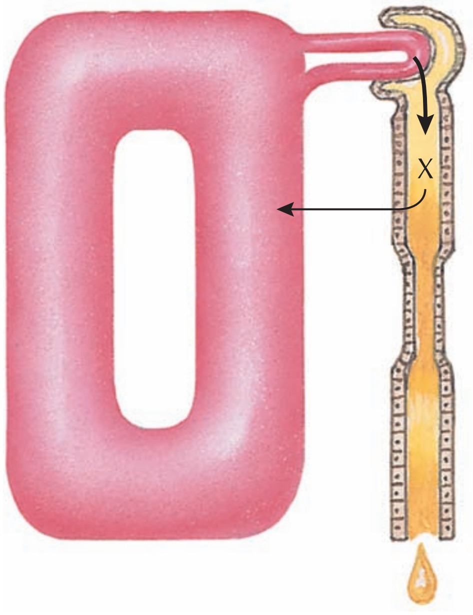
Clearance ratios greater than one suggest that X undergoes net secretion, whereas values less than one suggest that X undergoes net reabsorption.

In clinical practice, creatinine is used in lieu of inulin to calculate fractional excretion values (or clearance ratios) because it is an endogenous chemical that is generally at a steady-state concentration in plasma.

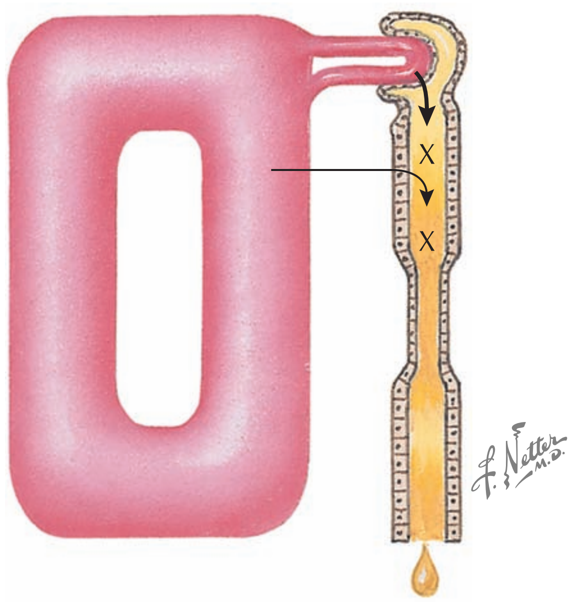
FRACTIONAL EXCRETION (CLEARANCE RATIOS)



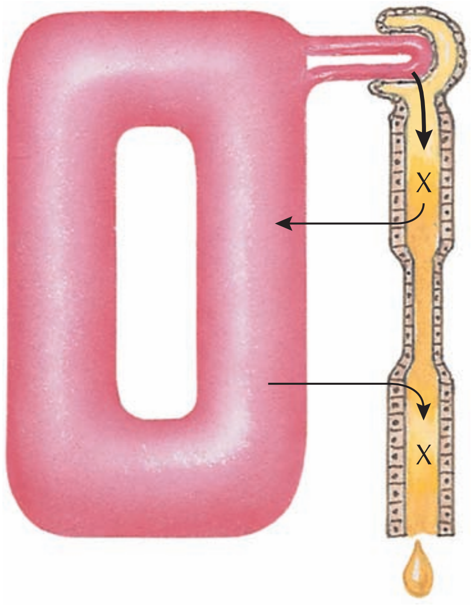
Substance X filtered at glomeruli, then neither reabsorbed nor secreted (e.g., inulin or creatinine).
C(x) = GFR
FE(x) = 1



Substance X filtered at glomeruli, then reabsorbed (e.g., sodium).
C(x) < GFR
FE(x) < 1

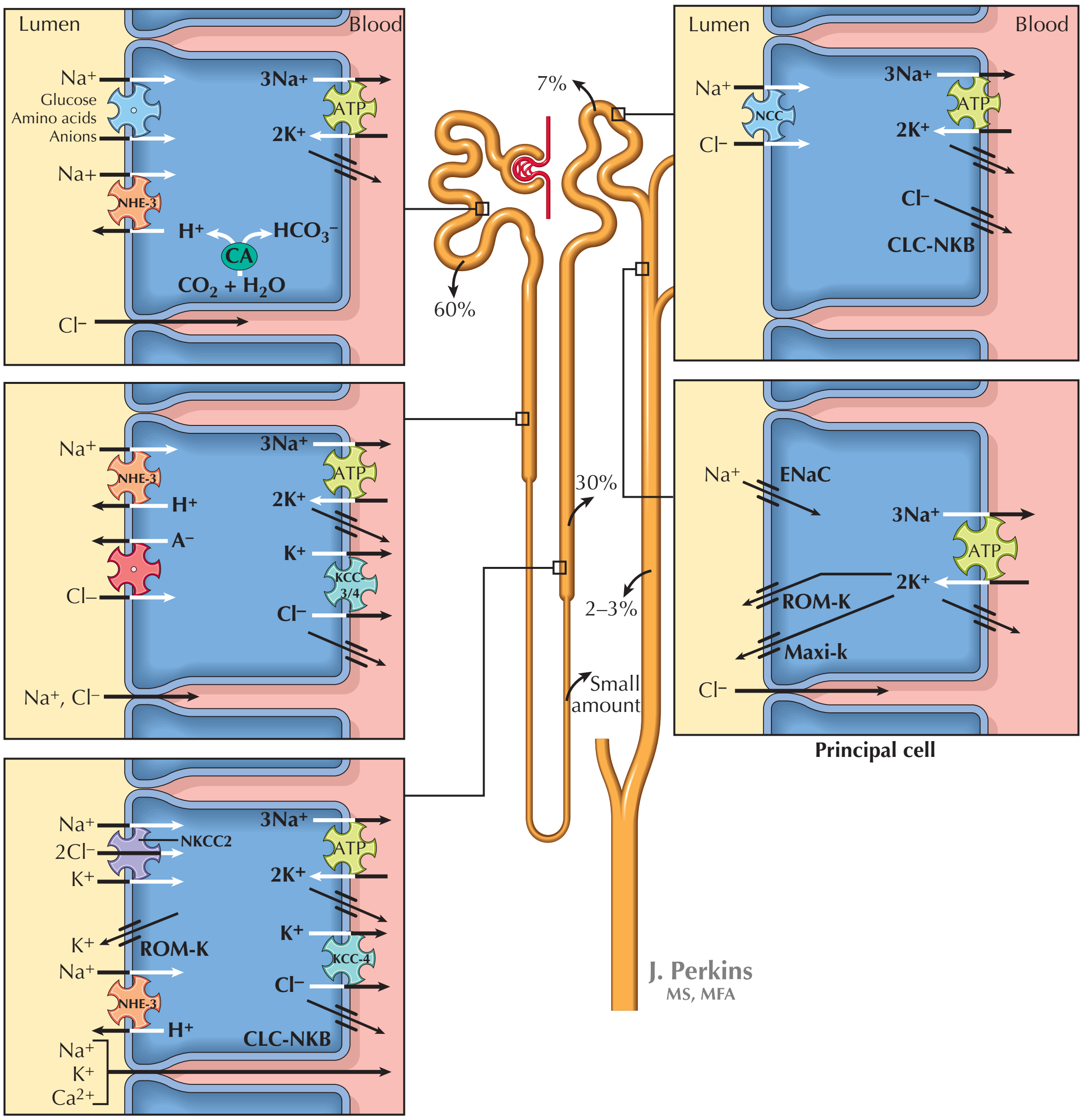


Substance X filtered at glomeruli, then secreted (e.g., PAH).
C(x) > GFR
FE(x) > 1



Substance X filtered at glomeruli, then both reabsorbed and secreted.
C(x) > or < GFR
FE(x) > or < 1

NEPHRON SITES OF SODIUM REABSORPTION



Examples of factors that affect sodium handling		
Factor	Effect	Mechanism
Norepinephrine Angiotensin II	↑Reabsorption	↑ NHE-3 transporter, Na+/K+ pump in proximal tubule
Aldosterone	↑Reabsorption	↑ ENaC channel in collecting duct ↑ NCC transporter in distal convoluted tubule
ADH (vasopressin)	↑Reabsorption	↑ NKCC2 transporter in thick ascending limb ↑ ENaC channel in collecting duct
ANP	↓Reabsorption	↓ NHE-3 transporter, Na+/K+ pump in proximal tubule ↓ ENaC channel in collecting duct

RENAL HANDLING OF SODIUM AND CHLORIDE

Sodium and chloride are both predominantly extracellular ions. In plasma, the sodium concentration is maintained between 135 to 145 mmol/L, whereas the chloride concentration is maintained between 98 to 108 mmol/L.

Both sodium and chloride are freely filtered at the glomerulus and almost completely (approximately 99%) reabsorbed. 60% of the filtered load is reabsorbed in the proximal tubule; 30% is reabsorbed in the thick ascending limb; 7% is reabsorbed in the distal convoluted tubule; and 2% to 3% is reabsorbed in the connecting tubule and collecting duct.

MECHANISMS OF TRANSPORT

In all portions of the nephron, basolateral Na^+/K^+ ATPases pump sodium from the tubular epithelial cells into the interstitium. As a result, intracellular sodium concentrations remain low, establishing a gradient for transcellular reabsorption.

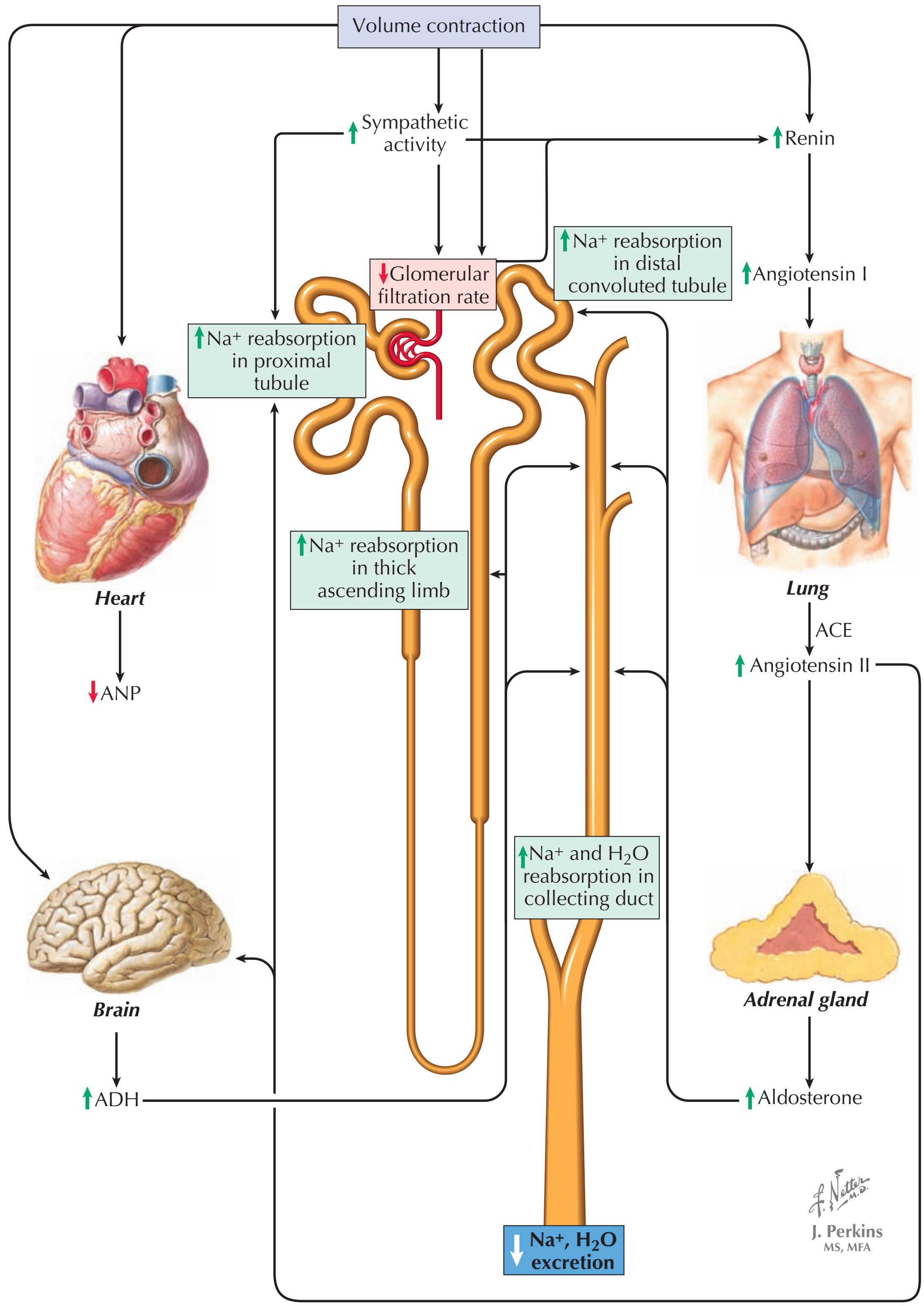
Proximal Tubule. Throughout the proximal tubule, sodium crosses the apical membranes of tubular epithelial cells on Na^+/H^+ exchangers (NHE-3), causing proton secretion by secondary active transport. To a lesser extent, sodium crosses apical membranes on symporters that transport one or more sodium ions in combination with various substances, including glucose, amino acids, phosphate, lactate, and citrate. The reabsorption of sodium, irrespective of the mechanism, transiently establishes an osmotic transepithelial gradient that promotes the passive, isotonic reabsorption of water (see Plate 3-15).

As sodium and water are reabsorbed, chloride becomes increasingly concentrated in proximal tubular fluid. In addition, the initial segment of the proximal tubular lumen has a negative charge. Thus there are chemical and electrical gradients favoring chloride reabsorption, which occurs along a paracellular pathway.

In later parts of the proximal tubule, the negative charge in the lumen dissipates, owing to extensive paracellular reabsorption of chloride. Instead, there is a positive charge, which creates an electrical gradient for the paracellular reabsorption of sodium. Despite this reversal, paracellular chloride reabsorption continues because of the strong chemical gradient in its favor. Some chloride also undergoes transcellular reabsorption via apical Cl^--anion antiporters, which are coupled with basolateral Cl^- channels and K^+/Cl^- cotransporters (KCC-3 and -4).

Thin Limb. The descending thin limb is impermeable to solutes but permits reabsorption of water, as discussed on Plate 3-15. Tubular fluid thus becomes concentrated in this segment, which establishes a chemical gradient favoring the reabsorption of some sodium

RESPONSE TO EXTRACELLULAR FLUID CONTRACTION


Volume contraction
↑ Sympathetic activity
↑ Renin
↑ Na+ reabsorption in distal convoluted tubule
↓ Glomerular filtration rate
↑ Angiotensin I
↑ Na+ reabsorption in proximal tubule
Heart
↑ Na+ reabsorption in thick ascending limb
Lung
ACE
↑ Angiotensin II
↓ ANP
↑ Na+ and H2O reabsorption in collecting duct
Brain
Adrenal gland
↑ ADH
↑ Aldosterone
↓ Na+, H2O excretion
F. Netter M.D.
J. Perkins MS, MFA

RENAL HANDLING OF SODIUM AND CHLORIDE *(Continued)*

and chloride from the ascending thin limb. Sodium undergoes paracellular reabsorption, whereas chloride undergoes transcellular reabsorption through apical and basolateral CLC-NKA channels.

Thick Ascending Limb. In this segment, sodium, chloride, and potassium undergo transcellular reabsorption together on an apical cotransporter (NKCC2). Two chloride ions are transported for each sodium and potassium ion. The basolateral Na^+/K^+ pumps establish a chemical gradient for sodium that drives this process.

Once in the cell, chloride crosses the basolateral membrane via channels (CLC-NKB) and K^+/Cl^- transporters (KCC-4). Potassium, in contrast, is recycled back into the lumen through apical ROM-K channels. The net result is a positive charge in the tubular lumen, which promotes the paracellular reabsorption of sodium and other cations.

Although the NHE-3 Na^+/H^+ exchanger is present in this segment, it makes only a minor contribution to overall sodium reabsorption and is more important for bicarbonate reabsorption (see Plate 3-21).

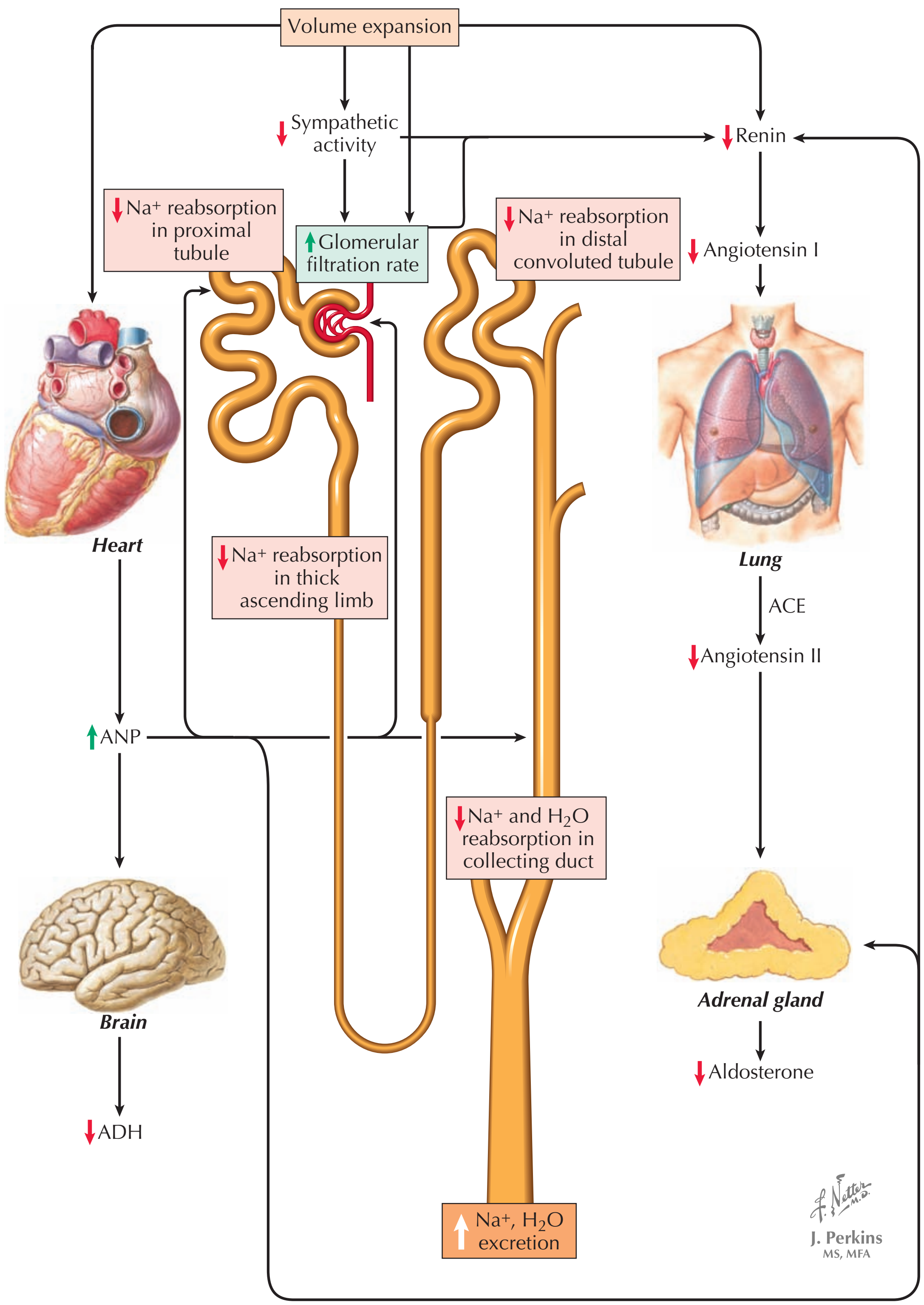
Distal Convoluted Tubule. In this segment, sodium and chloride undergo transcellular reabsorption together on an apical Na^+/Cl^- symporter (NCC). The basolateral Na^+/K^+ pumps establish a chemical gradient for sodium that drives this process. Once in the cell, chloride crosses the basolateral membrane via the CLC-NKB channel.

Connecting Tubule and Collecting Duct. In these segments, sodium undergoes transcellular reabsorption through apical channels (ENaC) located on principal cells. The reabsorption of sodium generates a negative charge in the tubular lumen, which creates a gradient for the paracellular reabsorption of chloride. Although not shown in the illustration, chloride also undergoes transcellular reabsorption across type B intercalated cells through an apical HCO_3^-/Cl^- exchanger (pendrin) and a basolateral channel (CLC-NKB).

REGULATION OF SODIUM HANDLING

Sodium is the principle osmole of extracellular fluid, and its plasma concentration is modulated by the systems that control the retention or excretion of free water. Thus an increase in sodium concentration results in the retention of free water, whereas a decrease in sodium concentration results in the excretion of free water. This mechanism is controlled by central osmoreceptors, which sense increases in osmolality and respond by promoting feelings of thirst, water-seeking behavior, and the release of antidiuretic hormone (ADH, or vasopressin). Through water consumption and the actions of ADH, which promotes water reabsorption from collecting ducts (see Plate 3-17), free

RESPONSE TO EXTRACELLULAR FLUID EXPANSION


Volume expansion
↓ Sympathetic activity
↓ Renin
↓ Na+ reabsorption in proximal tubule
↑ Glomerular filtration rate
↓ Na+ reabsorption in distal convoluted tubule
↓ Angiotensin I
Heart
Lung
ACE
↓ Angiotensin II
↓ Na+ reabsorption in thick ascending limb
↑ ANP
↓ Na+ and H2O reabsorption in collecting duct
Brain
Adrenal gland
↓ Aldosterone
↓ ADH
↑ Na+, H2O excretion
J. Perkins MS, MFA

RENAL HANDLING OF SODIUM AND CHLORIDE *(Continued)*

water is added to the extracellular fluid (ECF) until normal osmolality is restored. At this point, osmoreceptor activation ceases.

Because of this system, an increase or decrease in total body sodium will lead, by necessity, to expansion or contraction of the ECF volume. Free water intake, in contrast, does not affect ECF volume. First, free water distributes into both the intracellular and extracellular fluids. Second, dilution of the ECF after fluid intake suppresses ADH release, causing dilute urine to be produced until normal plasma osmolality is restored.

Because total body sodium is thus the primary determinant of ECF volume, the mechanisms that control ECF volume directly modulate the rate of sodium excretion in urine.

In the setting of ECF depletion, for example, several mechanisms increase the renal retention of sodium. Activation of baroreceptors in the aortic arch and carotid bodies, for example, causes an increase in sympathetic tone. Norepinephrine constricts afferent and efferent arterioles, which reduces the glomerular filtration rate, and it also stimulates NHE-3 transporters and Na^+/K^+ ATPases in the proximal tubule, which promotes sodium reabsorption. Meanwhile, renin release occurs secondary to multiple factors, including sympathetic input, decreased stretching of afferent arterioles, and decreased tubular flow rates. Renin catalyzes the synthesis of angiotensin II (AII), which has many effects that promote sodium retention. First, AII stimulates apical NHE-3 transporters and basolateral Na^+/K^+ ATPases in the proximal tubule. Second, AII promotes the release of aldosterone, which increases sodium reabsorption from the distal nephron by upregulating ENaC and NCC transporters. Third, AII promotes the release of ADH, which up-regulates sodium and water reabsorption from the collecting duct (by up-regulating ENaC and aquaporin channels) and the thick ascending limb (by upregulating NKCC2 transporters). Finally, AII constricts the efferent arteriole, which lowers hydrostatic pressure in the peritubular capillaries and, moreover, increases the filtration fraction, raising osmotic pressure in the peritubular capillaries. These altered forces both favor reabsorption from the proximal tubules.

In the setting of ECF overload, these various mechanisms are inactivated, promoting renal excretion of sodium. The effect is amplified by the release of atrial natriuretic peptide (ANP), which occurs in response to stretching of the cardiac atria. ANP dilates the afferent arteriole and constricts the efferent arteriole, which raises the glomerular filtration rate. In addition, it blocks sodium reabsorption from the proximal and distal tubules, as well as water reabsorption from the collecting duct. Finally, it suppresses the release of renin, aldosterone, and ADH.

RENAL HANDLING OF POTASSIUM

Potassium is a primarily intracellular ion, with skeletal muscle alone containing more than 75% of the body's total load. Less than 2% of this load is found in the extracellular fluid. The normal plasma concentration is between 3.5 and 5.0 mmol/L.

Extracellular potassium is freely filtered at the glomerulus. A large fraction of the filtered load is consistently reabsorbed along the proximal tubule (66%) and loop of Henle (25%). In the distal tubule, however, there is a variable degree of reabsorption or secretion that depends on input from homeostatic feedback mechanisms. In this manner, the kidneys make a crucial contribution to the regulation of the plasma potassium concentration.

TRANSPORT MECHANISMS

Proximal Tubule. In the proximal tubule, potassium is reabsorbed along a paracellular route. A chemical gradient is established as the reabsorption of sodium and water concentrates potassium in the tubular fluid. An electrical gradient is established as chloride is reabsorbed, which leaves a positive charge in the late part of the proximal tubule. There is some evidence that potassium also undergoes some transcellular reabsorption in this segment, but the details and relative importance of this pathway remain unknown.

Thick Ascending Limb. In the thick ascending limb, potassium undergoes transcellular reabsorption by crossing the apical membrane on the $Na^+/K^+/2Cl^-$ cotransporter (NKCC2), then crossing the basolateral plasma membrane via KCC4 K^+/Cl^- symporters and potassium channels. A subset of the potassium that enters the cells, however, is recycled back into the lumen through ROM-K channels. Such recycling creates a positive charge in the lumen that drives the paracellular reabsorption of potassium, sodium, and other cations.

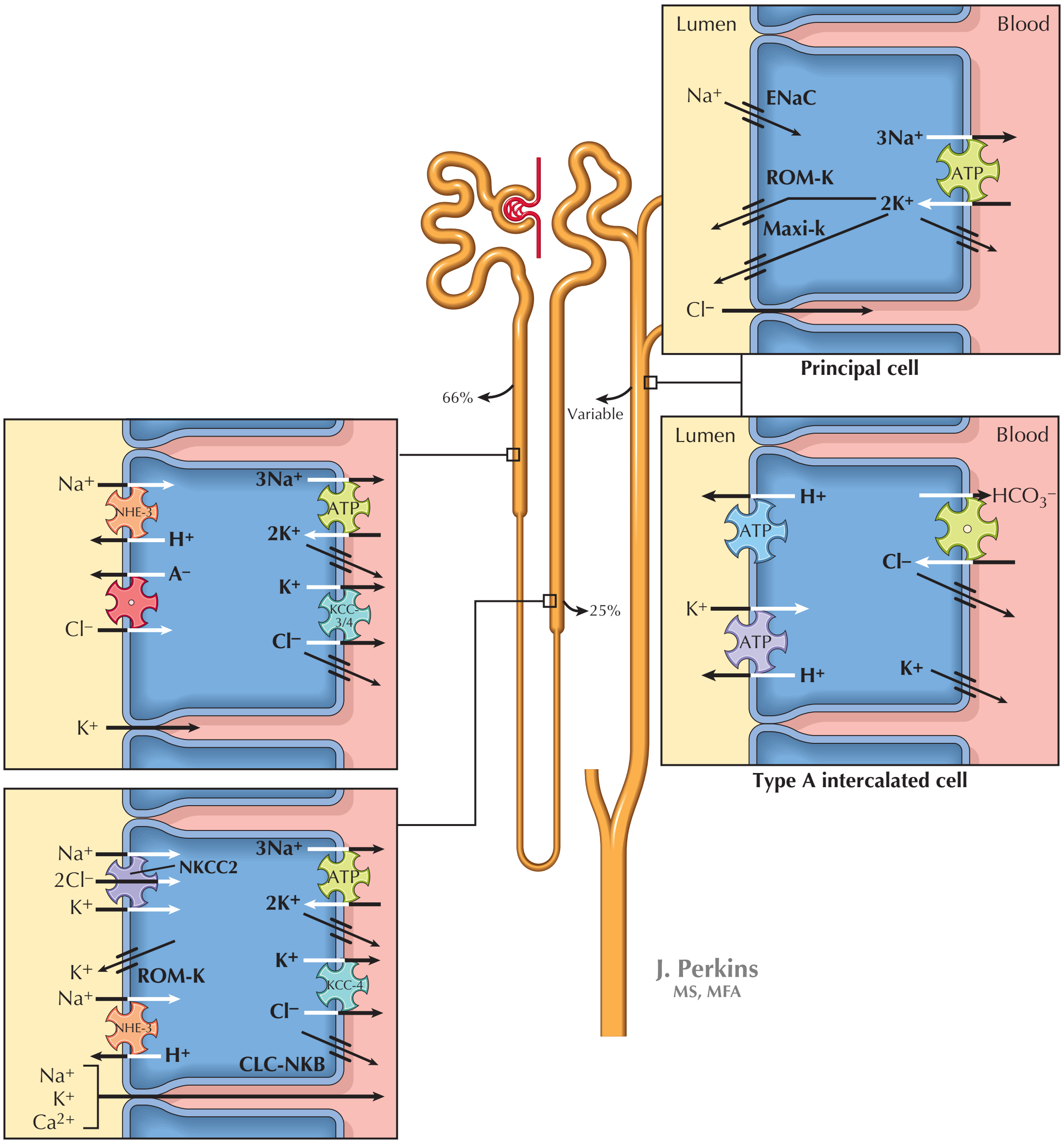
Distal Nephron. Potassium handling is more variable from the distal convoluted tubule onward, with overall excretion rates depending on the net balance of secretion and reabsorption.

Secretion occurs primarily in the connecting tubule and cortical collecting duct. When sodium enters principal cells through apical ENaC channels, a negative charge is left in the tubular lumen. An electrical gradient thus established, potassium that has been brought into principal cells on basolateral Na^+/K^+ ATPases flows into the lumen through apical ROM-K and maxi-K (also known as BK) channels. K^+ channels are also present in the basolateral compartment, as they are elsewhere in the nephron, to permit continuous operation of Na^+/K^+ ATPases.

Reabsorption occurs primarily in the outer medullary collecting duct. Type A intercalated cells possess apical H^+/K^+ antiport ATPases, which bring potassium into cells, and basolateral K^+ channels, which allow it to enter the interstitium.

REGULATION OF POTASSIUM EXCRETION

Hyperkalemia promotes the release of aldosterone from the adrenal cortex, which up-regulates apical ENaC and basolateral Na^+/K^+ ATPases in principal cells. The resulting increase in sodium reabsorption enhances the electrical gradient for potassium secretion. Hyperkalemia also causes direct, aldosterone-independent stimulation of ENaC and ROM-K channels in principal cells, further enhancing potassium secretion.



Examples of factors that affect potassium handling

Factor	Effect	Mechanism
Hyperkalemia	↑Secretion	↑Aldosterone → ↑ENaC ↑Na^+/K^+ pump ↑ROM-K (all in principal cells)
Hypokalemia	↓Secretion	↓Aldosterone → ↓ENaC ↓Na^+/K^+ pump ↓ROM-K (all in principal cells)
Acidosis	↑Reabsorption	↑H^+/K^+ pump (intercalated cells)
	↓Secretion	Basolateral H^+/K^+ exchange->↓$[K]_{intracellular}$ (not shown)
Alkalosis	↑Secretion	Basolateral H^+/K^+ exchange->↑$[K]_{intracellular}$ (not shown)

Hypokalemia, in contrast, suppresses aldosterone release and down-regulates apical ROM-K channels in principal cells, thereby reducing potassium secretion. In addition, hypokalemia enhances expression of apical H^+/K^+ ATPases in type A intercalated cells, promoting potassium reabsorption.

Acid-base disturbances also alter potassium secretion or reabsorption, largely because of basolateral H^+/K^+ exchange. In acidosis, protons enter cells to be buffered, and potassium ions exit cells to maintain electroneutrality. The reduction in intracellular potassium levels decreases the chemical gradient for secretion into the tubules. In alkalosis, in contrast, protons exit cells, causing a rise in intracellular potassium levels that promotes secretion.

Finally, volume status has an important relationship with potassium handling. In volume contraction, AII promotes release of aldosterone, which enhances potassium secretion. In volume expansion, increased flow rates through the nephron stimulate greater potassium secretion through maxi-K channels. Thus potassium secretion is ensured during both volume expanded and contracted states.

RENAL HANDLING OF CALCIUM, PHOSPHATE, AND MAGNESIUM

CALCIUM

More than 98% of total body calcium is in bones, whereas the remainder is located in intracellular and extracellular fluid. Normal plasma concentrations, which range from 8.8 to 10.3 mg/dL, are maintained by the actions of PTH, 1,25-hydroxyvitamin D, and calcitonin on bones, the gastrointestinal tract, and the kidneys.

About half of the extracellular calcium load is in an active, ionized form, whereas the remainder complexes with albumin and other anions. The ionized calcium is freely filtered at the glomerulus, and normally almost all of it is reabsorbed.

In the proximal tubule, 50% to 60% of the filtered load is reabsorbed along a paracellular route. A chemical gradient is established as sodium and water are reabsorbed, concentrating calcium in the tubular fluid. Meanwhile, an electrical gradient is established by the paracellular reabsorption of chloride, which leaves a positive charge in the lumen. Specialized tight junction proteins, such as claudin-2, may form a cation-specific paracellular pathway.

In the thick ascending limb, 15% of the filtered load is reabsorbed along a paracellular route. An electrical gradient, formed secondary to K^+ recycling, drives this process. Claudin-16, another tight junction protein, is an important component of this paracellular pathway, and mutations are associated with familial hypomagnesemia with hypocalciuria.

In the distal convoluted and connecting tubules, 10% to 15% of the filtered load is reabsorbed along a transcellular route. Calcium crosses the apical membrane through TRPV5 channels, binds to calbindin, then exits the basolateral membrane on the NCX1 Na^+/Ca^{2+} exchanger and, to a lesser degree, a Ca^{2+} ATPase (PMCA).

The collecting duct makes an unknown, but likely minor, contribution to calcium reabsorption.

Hypocalcemia triggers release of PTH, which has numerous effects on renal function. In the proximal tubule, it inhibits the NHE-3 Na^+/H^+ exchanger, reducing the gradient for paracellular calcium reabsorption. (This seemingly paradoxical effect allows PTH to increase phosphate excretion, as discussed later.) In the distal nephron, however, it up-regulates the apical TRPV5 calcium channel, causing a net increase in calcium reabsorption. Meanwhile, hypercalcemia both suppresses PTH release and directly inhibits calcium reabsorption. In the thick ascending limb, for example, the increased load of reabsorbed calcium activates a basolateral calcium-sensing receptor (CaSR), which then inhibits NKCC2 transporters and ROM-K channels, reducing the electrical gradient for calcium reabsorption.

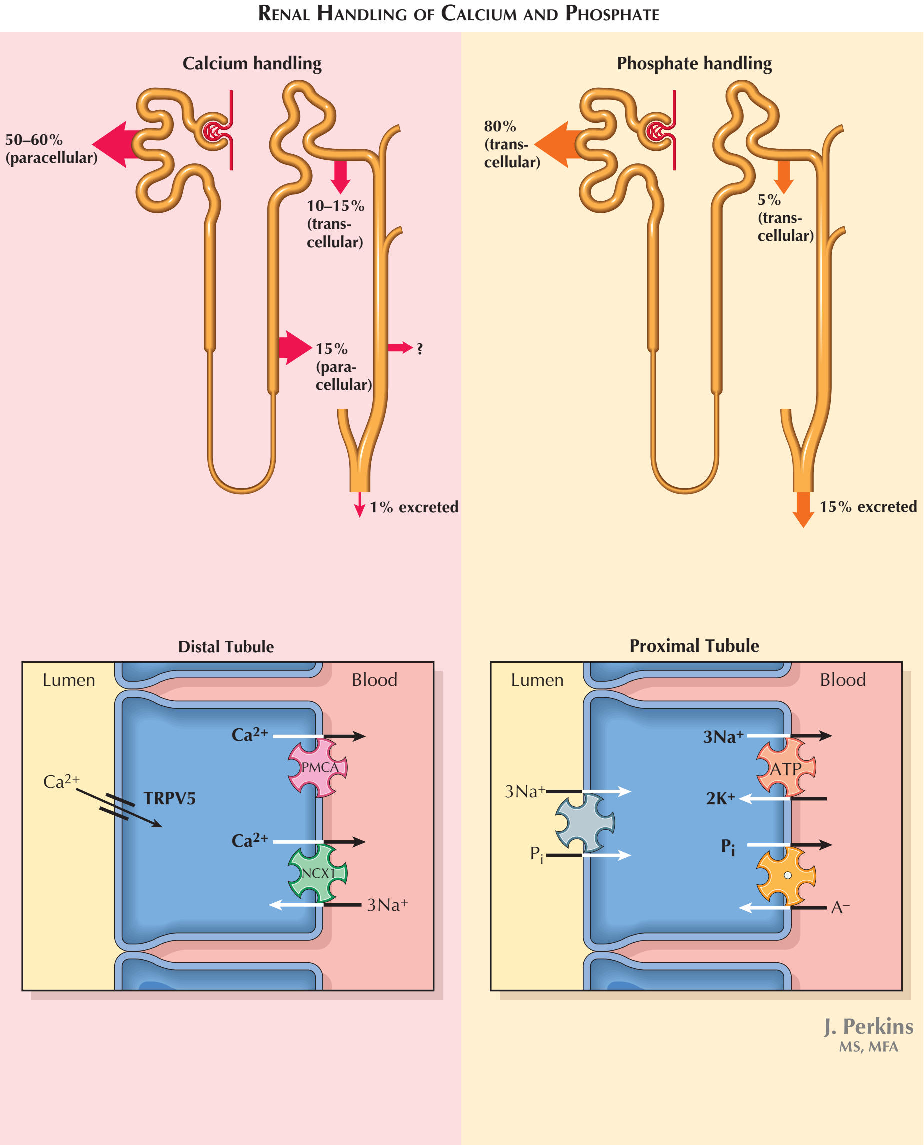
Finally, acidosis inhibits the TRPV5 calcium channel, whereas alkalosis has the opposite effect.

PHOSPHATE

About 85% of total body phosphate is stored in bones, 14% in soft tissues, and 1% in extracellular fluid. Normal plasma concentrations, which range from 3 to 4.5 mg/dL, are maintained by the actions of PTH, 1,25-hydroxyvitamin D, and phosphatonins on the parathyroid glands, bones, gastrointestinal tract, and kidneys.

About 90% of plasma phosphate is unbound and freely filtered at the glomerulus. About 85% of the filtered load is normally reabsorbed.

RENAL HANDLING OF CALCIUM AND PHOSPHATE



Modulation of Ca^{2+} reabsorption

Factor	Nephron Site	Mechanism	Effect
↑ PTH	DCT	↑ TRPV5 channels	↑
	Proximal tubule	↓ NHE-3 transporters	
↑ Plasma $[Ca^{2+}]$	Thick ascending limb	↑ CaSR	↓

Modulation of P_i reabsorption

Factor	Nephron Site	Mechanism	Effect
↑ PTH	Proximal tubule	↓ Na/P_i symporter	↓
↑ FGF-23	Proximal tubule	↓ Na/P_i symporter	↓
↑ P_i intake	Proximal tubule	↓ Na/P_i symporter	↓

In the proximal tubule, 80% of the filtered load is reabsorbed along a transcellular route. Phosphate crosses the apical membrane on Na^+/P_i symporters. The pathway of basolateral exit is poorly understood but may involve a phosphate/anion exchanger.

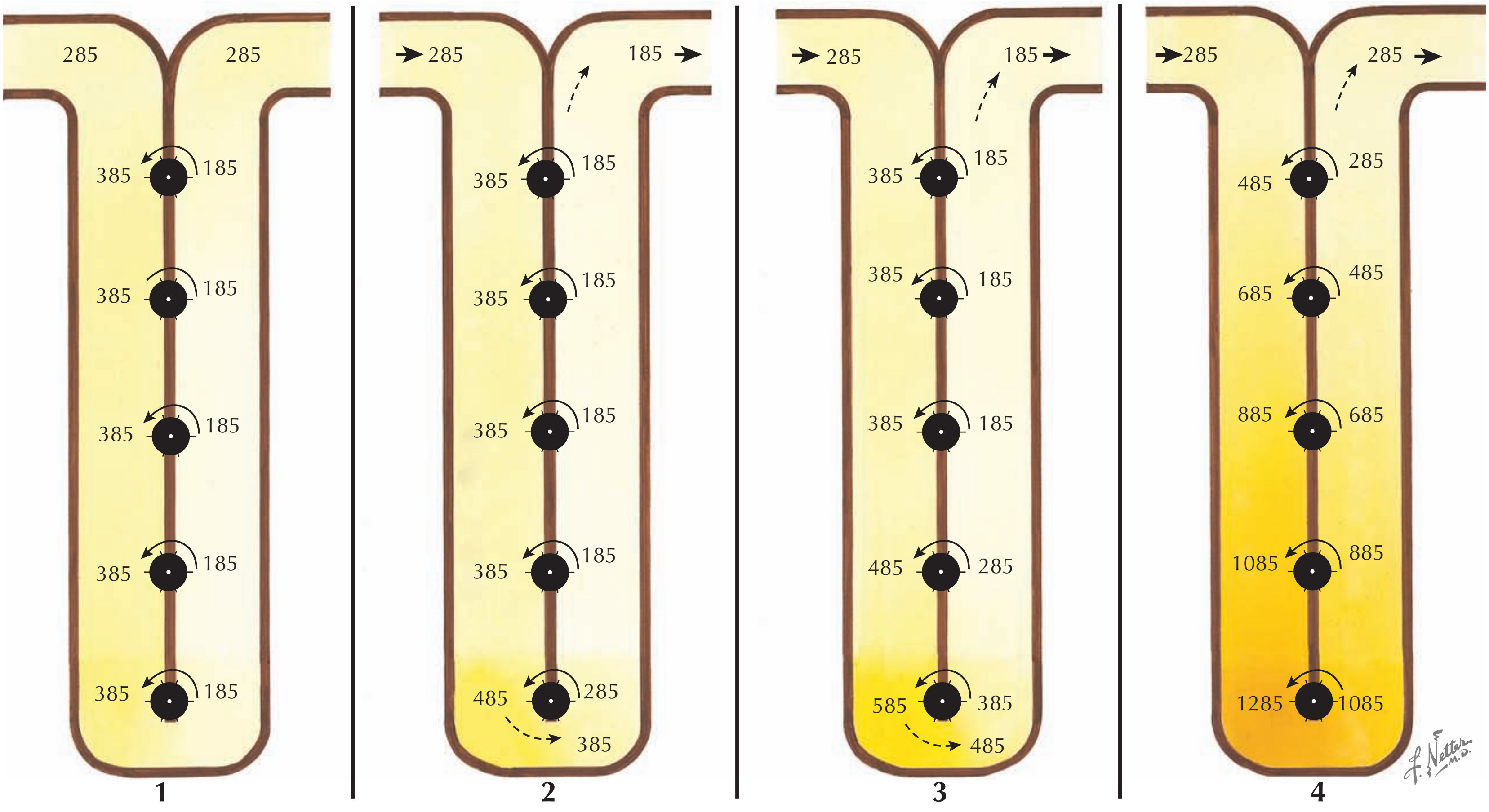
In the distal convoluted tubule and connecting tubule, 5% of the filtered load is reabsorbed along a transcellular route that remains poorly understood.

Hyperphosphatemia promotes release of PTH, which down-regulates Na^+/P_i symporters and basolateral Na^+/K^+ ATPases in the proximal tubule. As a result, phosphate reabsorption is suppressed. Additionally, hyperphosphatemia causes the release of FGF-23 from osteocytes and osteoblasts in bone, which causes decreased Na^+/P_i expression. Finally, increased dietary phosphate intake appears to directly down-regulate Na^+/P_i transport through a PTH-independent mechanism. Hypophosphatemia, meanwhile, causes the opposite effects.

MAGNESIUM

About half of total body magnesium is in bone, and nearly all of the remainder is in intracellular fluid. Only 1% is in the extracellular space, with normal plasma concentrations ranging from 1.8 to 2.3 mg/dL. About 80% of the extracellular load is unbound to proteins and freely filtered at the glomerulus. About 95% to 98% of the filtered load is normally reabsorbed. 20% is reabsorbed in the proximal tubule via an unknown, likely passive, mechanism. Another 60% to 70% is reabsorbed in the thick ascending limb through a paracellular route, driven by the electrical gradient resulting from K^+ recycling. Claudin 16 is thought to form the pore for paracellular magnesium reabsorption. Finally, 5% to 10% of the filtered load is reabsorbed in the distal nephron through an apical Mg^{2+} channel known as TRPM6. The pathway for basolateral exit is not known.

MODEL OF THE COUNTERCURRENT MULTIPLIER: PART I



COUNTERCURRENT MULTIPLICATION

The countercurrent multiplier system is a sophisticated apparatus that evolved in mammals and birds to conserve water. It forms a longitudinal concentration gradient in the medullary interstitium that increases in strength toward the papilla. This gradient is crucial for water reabsorption from the renal tubules, which is a passive process that depends on osmotic pressure from the interstitium.

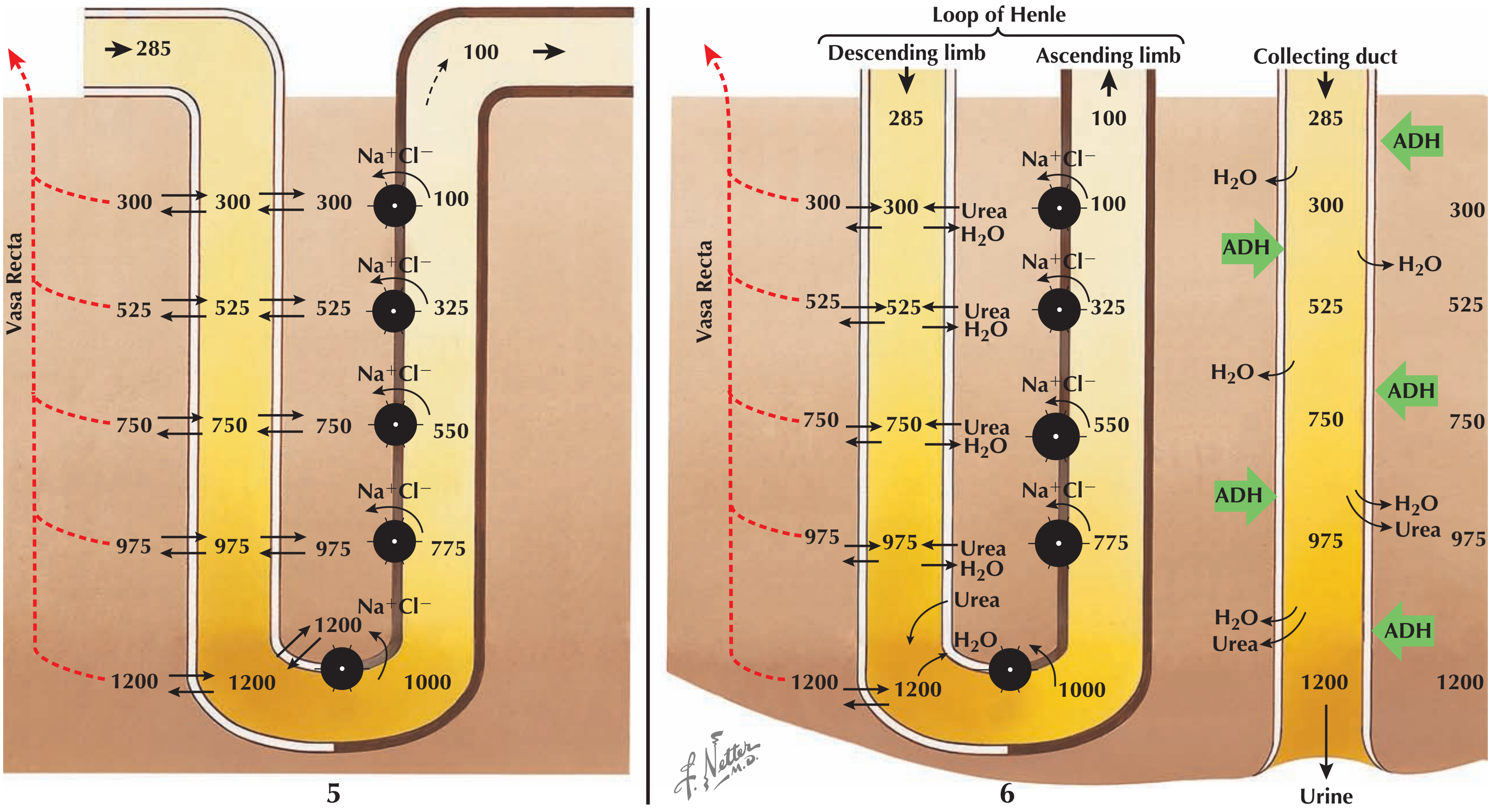
The creation and maintenance of this gradient is best understood by first considering a simplified model of the loop of Henle. In this model, a tube of fluid is divided by a membrane in all but its most inferior aspect. The left side represents the entire descending limb, whereas the right side represents the entire ascending limb. Fluid enters at the top of the left-sided column, travels beneath the membrane, and then exits at the top of the right-sided column. The dividing membrane is impermeable to water but contains active transporters, which pump solute from the ascending limb to the descending limb. These transporters are powerful enough to establish a transmembrane gradient of about 200 milliosmoles (mOsm).

In Panel 1, the entire tube is filled with fluid concentrated at 285 mOsm, which is roughly equal to the osmolality of filtrate as it enters the descending limb. A transmembrane gradient is established as the transporters pump solute across the membrane.

In Panel 2, fluid begins to move through the circuit. Thus, at the hairpin turn, concentrated fluid from the descending limb mixes with less concentrated fluid from the ascending limb. As a result, a fluid of average concentration is formed. Because the active transporters can establish a 200 mOsm gradient, the last part of the descending limb becomes correspondingly more concentrated.

In Panel 3, the flow process continues, and as concentrated fluid continues to rise in the ascending limb, reestablishment of the 200 mOsm transmembrane gradient causes a corresponding rise in the concentration

MODEL OF THE COUNTERCURRENT MULTIPLIER: PART II


285
100
Vasa Recta
Na+Cl−
300
300
300
100
525
525
525
325
750
750
750
550
975
975
975
775
1200
1200
1200
1000
5
Loop of Henle
Descending limb
Ascending limb
Collecting duct
Vasa Recta
285
100
285
ADH
H₂O
300
300
Urea
H₂O
Na+Cl−
100
300
300
ADH
H₂O
525
525
Urea
H₂O
325
525
525
H₂O
ADH
750
750
Urea
H₂O
550
750
750
ADH
H₂O
Urea
975
975
Urea
H₂O
775
975
975
Urea
H₂O
H₂O
Urea
ADH
1200
1200
1000
1200
1200
Urine
6
F. Netter M.D.

COUNTERCURRENT MULTIPLICATION *(Continued)*

of fluid in the descending limb. At this stage, solute is still being retained within the system, and thus the outgoing fluid is less concentrated than the incoming fluid.

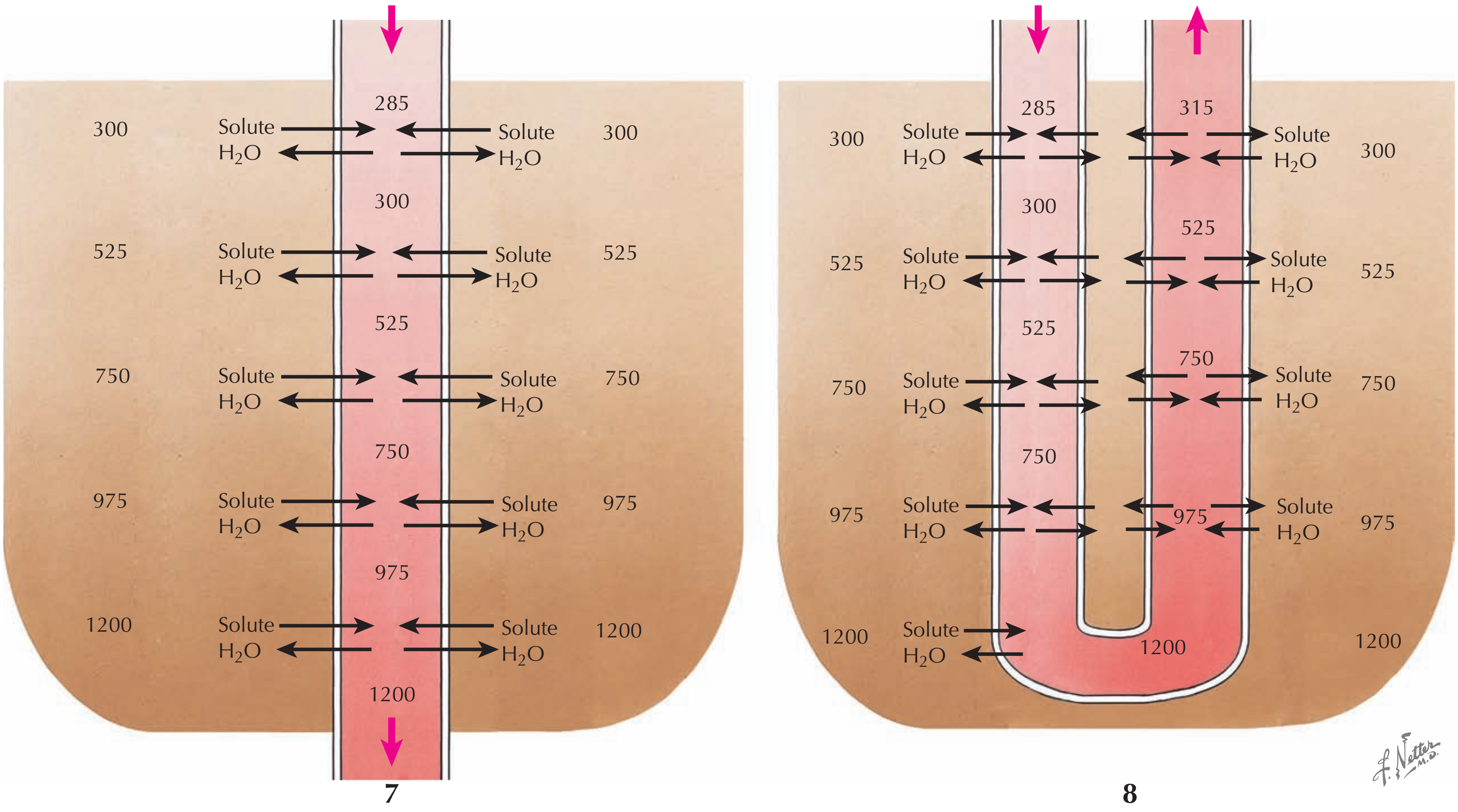
In Panel 4, steady state has been reached, meaning that no additional solute is being added to the system. Thus the incoming and outgoing fluid are iso-osmotic. The overall effect of this process has been to establish high longitudinal gradients, whereas the transmembrane gradient is comparatively small.

In Panel 5, which represents the actual loop of Henle, these same events occur but with important differences. First, the limbs are separated by an interstitium, rather than a single membrane. The ascending limb is impermeable to water but reabsorbs solutes into the interstitium. The descending limb, in contrast, is permeable to water but not to solutes. As a result, the concentration of fluid in the descending limb rapidly equilibrates with the concentration in the interstitium. Another difference is that the fluid leaving the loop of Henle is hypo-osmotic to the fluid coming in, reflecting the fact that a small amount of solute is continuously lost from the interstitium, preventing a steady state from being reached.

In Panel 6, the collecting duct is added to the model and runs parallel to the loop of Henle. In the presence of ADH (see Plate 3-17), the collecting duct becomes permeable to water, which is reabsorbed from the collecting duct lumen into the interstitium. This process is entirely passive, depending on the osmotic pressure of the interstitium. Thus the maximum concentration in the medullary interstitium determines the maximum concentration of the final urine.

The addition of the collecting duct also illustrates how urea contributes to formation of the interstitial concentration gradient, especially in the inner medulla. In the presence of ADH, the inner medullary collecting duct becomes permeable to urea. As water is reabsorbed from the cortical and outer medullary collecting ducts, urea becomes highly concentrated within the tubular fluid. Once the inner medulla is reached, urea flows out

MODELS TO DEMONSTRATE PRINCIPLE OF COUNTERCURRENT EXCHANGE SYSTEM OF VASA RECTA IN MINIMIZING DISSIPATION OF MEDULLARY OSMOTIC GRADIENT



285
300
Solute
H_2O
Solute
H_2O
300
300
525
Solute
H_2O
Solute
H_2O
525
525
750
Solute
H_2O
Solute
H_2O
750
750
975
Solute
H_2O
Solute
H_2O
975
975
1200
Solute
H_2O
Solute
H_2O
1200
1200
7
285
315
300
Solute
H_2O
Solute
H_2O
300
300
525
525
Solute
H_2O
Solute
H_2O
525
525
750
750
Solute
H_2O
Solute
H_2O
750
750
975
975
Solute
H_2O
Solute
H_2O
975
1200
Solute
H_2O
1200
1200
8

COUNTERCURRENT MULTIPLICATION *(Continued)*

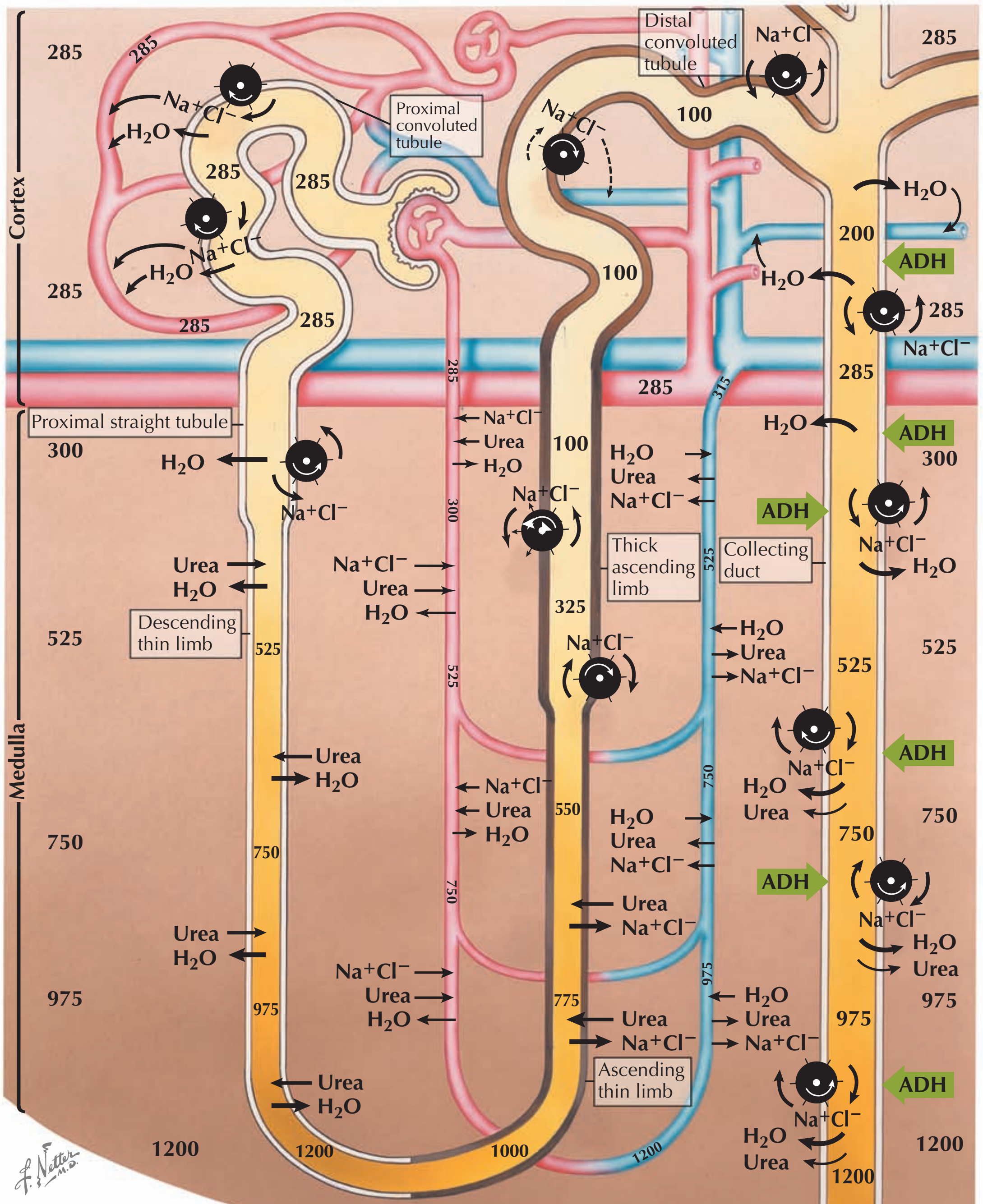
of the collecting duct and accumulates in the interstitium, contributing to the concentration gradient. Thus, as further described on Plate 3-17, ADH not only promotes water reabsorption from the collecting duct, but it also activates mechanisms that strengthen the concentration gradient, thereby ensuring water reabsorption is maximal.

Once deposited in the interstitium, some urea drifts from the inner medulla and is secreted back into the proximal tubule and loop of Henle. By reentering the tubular fluid in this manner, urea is returned to the inner medullary collecting duct to once again be reabsorbed. This process, known as urea recycling, tends to minimize urea depletion from the inner medulla.

The final elements that need to be added to this model are the capillaries of the vasa recta, which are permeable to water. If these vessels passed straight through the interstitium (Panel 7), osmotic pressure would draw out plasma and dilute the concentration gradient. Instead, the capillaries turn back upon themselves (Panel 8), and thus water that effluxes from the descending capillaries is reabsorbed in the ascending capillaries. This process is known as countercurrent exchange.

The blood leaving the medulla, however, does not completely reabsorb all of the effluxed plasma. Thus outgoing blood is slightly hyperosmotic compared with incoming blood. As a result, the anatomic configuration of the vasa recta minimizes, but does not completely prevent, solute loss from the medulla. These losses are also small, because the blood flow to the medulla is very low. Release of ADH further constricts the vasa recta capillaries, ensuring maintenance of the high interstitial concentrations required for maximal urine concentration.

URINE CONCENTRATION IN LONG-LOOPED NEPHRON (ADH PRESENT)


Cortex
Medulla
285
285
Na+Cl−
H_2O
285
285
Proximal convoluted tubule
285
285
285
Na+Cl−
H_2O
Distal convoluted tubule
Na+Cl−
285
Na+Cl−
100
100
H_2O
200
ADH
H_2O
285
Na+Cl−
285
285
315
285
Proximal straight tubule
300
H_2O
Na+Cl−
Na+Cl−
Urea
H_2O
100
H_2O
Urea
Na+Cl−
H_2O
ADH
300
300
Na+Cl−
ADH
Urea
H_2O
Na+Cl−
Urea
H_2O
Thick ascending limb
525
Collecting duct
Na+Cl−
H_2O
Descending thin limb
525
525
325
H_2O
Urea
Na+Cl−
Na+Cl−
525
525
525
Urea
H_2O
Na+Cl−
Urea
H_2O
550
H_2O
Urea
Na+Cl−
750
ADH
Na+Cl−
H_2O
Urea
750
750
750
750
Urea
Na+Cl−
ADH
Urea
H_2O
Na+Cl−
Urea
H_2O
Na+Cl−
H_2O
Urea
975
975
775
Urea
Na+Cl−
975
H_2O
Urea
Na+Cl−
975
975
Ascending thin limb
Urea
H_2O
ADH
Na+Cl−
H_2O
Urea
1200
1200
1000
1200
1200
1200
F. Netter M.D.

Note: Figures given are exemplary rather than specific

▬ Water impermeable (aquaporins absent)

▭ Water permeable (aquaporins present)

URINE CONCENTRATION AND DILUTION AND OVERVIEW OF WATER HANDLING

In normal kidneys more than 180 liters of fluid are filtered into the nephrons each day, but nearly all of it is reabsorbed into the peritubular circulation.

Tight junctions form a watertight seal between tubular epithelial cells throughout most of the nephron. Thus, water reabsorption occurs primarily through a transcellular route, requiring specialized channels known as aquaporins (AQPs) in both the apical and basolateral compartments of the plasma membrane.

Because aquaporins are channels, and not pumps, the reabsorption of water is a passive process, dependent on osmotic pressure from solutes concentrated in the surrounding interstitium.

In each tubular segment, the reabsorption of water can be greater than, less than, or equal to the reabsorption of solutes. As a result, urine becomes more concentrated as it passes through some segments and more diluted as it passes through others. The final concentration of excreted urine is determined in the collecting duct, which reflects not only the fact that this segment is located at the end of the nephron, but also that it reabsorbs water at a variable rate based on hormonal input.

Proximal Tubule. The proximal tubule reabsorbs two thirds of the filtered water. There is a large gradient for water reabsorption from this segment because of the high rate of solute reabsorption. As solute begins to accumulate in the interstitium, water crosses from the tubular lumen to the interstitium through AQP-1 channels in both the apical and basolateral plasma membranes.

Because water reabsorption from the proximal tubule is directly dependent on the rate of solute reabsorption, and because AQP-1 channels are always present, the filtrate remains iso-osmotic to plasma as it passes through this segment.

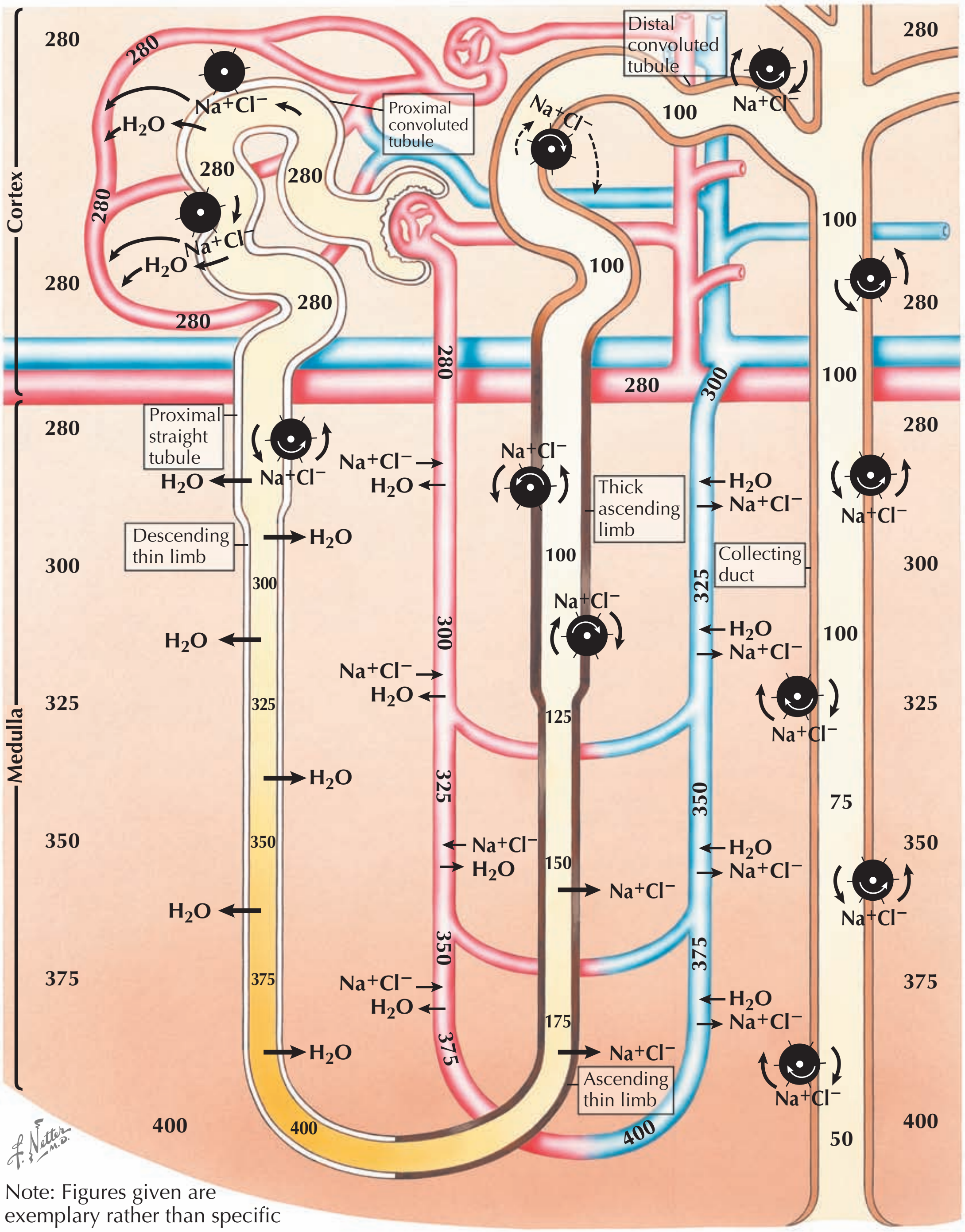
Descending Thin Limb. The descending thin limb reabsorbs an additional fraction of the filtered water. There is a large gradient for water reabsorption from this segment even though it reabsorbs only a small amount of solute. This gradient reflects the high rates of reabsorption from the thick ascending limb, which is adjacent to the ascending thin limb and adds solute to its surrounding interstitium. As in the proximal tubule, water crosses the tubular epithelium through AQP-1 channels.

As described on Plate 1-24, the descending thin limbs of short-looped (cortical) and long-looped (juxtamedullary) nephrons differ not only in length but also in cellular composition. In short-looped nephrons, the descending thin limb consists of type I cells, whereas in long-looped nephrons, it consists of type II cells in the outer medulla and type III cells in the inner medulla. Type I and II cells are more permeable to water than type III cells. Thus, in long-looped nephrons, water reabsorption from the descending thin limb decreases near the inner medulla.

Because water reabsorption exceeds solute reabsorption in the descending thin limb, tubular fluid becomes more concentrated. This process, however, is not under tight control. As a result, the descending thin limb does not have a major role in determining the final concentration of excreted urine.

Ascending Thin Limb and Thick Ascending Limb. The ascending thin limb (found only in long-looped nephrons) and thick ascending limb do not contain

URINE DILUTION IN LONG-LOOPED NEPHRON (ADH ABSENT)



Note: Figures given are exemplary rather than specific

▬ Water impermeable (aquaporins absent)

▭ Water permeable (aquaporins present)

URINE CONCENTRATION AND DILUTION AND OVERVIEW OF WATER HANDLING *(Continued)*

aquaporin channels and are therefore impermeable to water. The extensive reabsorption of solutes from these segments, however, dilutes tubular fluid and establishes a concentration gradient for water reabsorption from adjacent segments, such as the descending thin limb and collecting duct.

Because the dilution process in the ascending limb is not under tight control, this segment does not have a major role in determining the final concentration of excreted urine.

Distal Convoluted Tubule. Like the thick ascending limb, the distal convoluted tubule reabsorbs solutes but is impermeable to water. Therefore, this segment dilutes tubular fluid but, for the same reasons as the thick ascending limb, does not have a major role in determining the final concentration of excreted urine.

Connecting Tubule and Collecting Duct. The connecting tubule and collecting duct reabsorb a variable volume of filtered water, which determines the final concentration of excreted urine.

By reabsorbing more or less free water from the urine, these segments can dilute or concentrate plasma, helping to offset the changes in osmolality that result from inconsistent intake of water and salt over the course of each day. The hormone that controls water reabsorption is known as antidiuretic hormone (ADH, or vasopressin).

In response to increases in plasma osmolality, ADH is released from the posterior pituitary. In the connecting tubule and collecting duct this hormone causes vesicles containing AQP-2 channels to fuse with the apical plasma membrane of principal cells. Since AQP-4 channels are always present in the basolateral plasma membrane of these cells, the insertion of AQP-2 channels is sufficient to cause a dramatic increase in water reabsorption.

Because of the countercurrent multiplier system, there is a strong gradient for water reabsorption from the collecting duct that increases in strength toward the papillae. Because water reabsorption is a passive process, the maximum achievable urine concentration is equal to the peak osmolality in the medullary interstitium, about 1200 mOsm/kg H_2O. Such concentrations are only achievable in long-looped nephrons, however, because short-looped nephrons do not reach the inner medulla.

In addition to its direct effects on aquaporin channels, ADH has several actions that enhance the countercurrent system and thus increase the gradient for water reabsorption. In particular, this hormone increases solute reabsorption from the thick ascending limb, constricts vasa recta capillaries to reduce solute washout, and increases urea reabsorption from the inner medullary collecting duct. Some of the urea that drifts toward the cortex is secreted back into more proximal segments of the renal tubules so that it can be deposited again in the inner medulla.

In response to decreases in plasma osmolality, ADH release is inhibited, and AQP-2 channels are consequently endocytosed. The lack of water reabsorption from the collecting duct, coupled with the ongoing reabsorption of sodium from this segment, dilutes the urine to a minimum osmolality of 50 mOsm/kg H_2O.

Over the course of several hours, variable input from the ADH system leads to accumulation of urine in the bladder that has an osmolality between 50 and 1200 mOsm/kg H_2O. In patients with abnormal serum sodium concentrations, measurement of the urine osmolality can indicate whether the defect lies in the urine concentration process or elsewhere.

ANTIDIURETIC HORMONE

ADH, also known as vasopressin, plays a crucial role in maintaining the normal osmolality of extracellular fluid, which depends primarily on the extracellular sodium concentration. ADH exerts its effect by altering the osmolality of excreted urine, which can range from 50 to 1200 mOsm/kg H_2O.

When plasma osmolality increases, ADH release causes extensive water reabsorption in the distal nephron. As a result, the urine becomes highly concentrated, and the plasma consequently becomes more dilute. In contrast, when plasma osmolality decreases, inhibition of ADH release prevents water reabsorption in the distal nephron, leading to dilution of urine and concentration of plasma.

MECHANISMS OF RELEASE

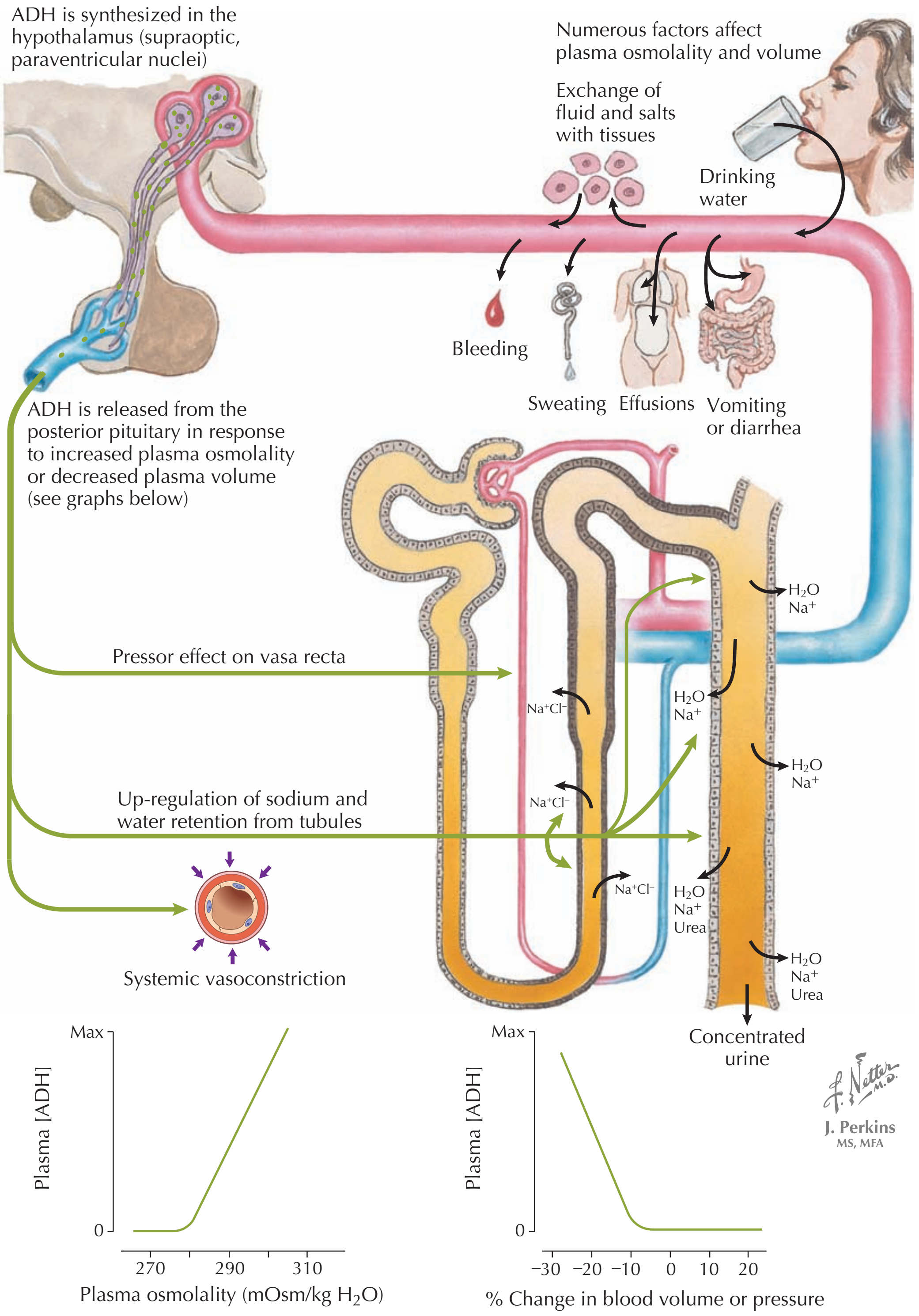
ADH is produced in the supraoptic and paraventricular nuclei of the hypothalamus. It is then conveyed along axons to the posterior pituitary for storage and release.

ADH release occurs primarily in response to activation of osmoreceptors in the anterior hypothalamus. These receptors, located outside of the blood-brain barrier, are extremely sensitive to changes in plasma osmolality. Their activation has been hypothesized to occur when there is a loss of intracellular fluid secondary to increased extracellular osmotic pressure. In support of this hypothesis, the osmoreceptors are not equally sensitive to all solutes. Sodium, for example, reliably activates osmoreceptors at high concentrations because, as a predominantly extracellular ion, it establishes a transmembrane osmotic gradient. In contrast, urea and glucose generally do not activate osmoreceptors even at high concentrations because they freely enter cells, thus failing to establish an osmotic gradient. When patients experience extreme insulin depletion, however, osmoreceptors may become sensitive to high concentrations of glucose, presumably because of its increased restriction to the extracellular space.

ADH is also released in response to intravascular volume depletion. In this setting, the primary objective is to retain intravascular volume, rather than to adjust plasma osmolarity. Such release is mediated by baroreceptors in the atria, aorta, and carotid sinus, which send afferent signals to the brain along the vagus and glossopharyngeal nerves. This sensing mechanism is not nearly as sensitive as the osmolality-sensing apparatus, however, and does not become active until 5% to 10% of plasma volume has been lost.

Finally, ADH is also released in response to increased levels of angiotensin II (AII), a hormone released during renal hypoperfusion (see Plate 3-18).

MECHANISM OF ANTIDIURETIC HORMONE IN REGULATING URINE VOLUME AND CONCENTRATION


ADH is synthesized in the hypothalamus (supraoptic, paraventricular nuclei)
Numerous factors affect plasma osmolality and volume
Exchange of fluid and salts with tissues
Drinking water
Bleeding
Sweating
Effusions
Vomiting or diarrhea
ADH is released from the posterior pituitary in response to increased plasma osmolality or decreased plasma volume (see graphs below)
Pressor effect on vasa recta
Up-regulation of sodium and water retention from tubules
Systemic vasoconstriction
H_2O Na^+
Na^+Cl^-
H_2O Na^+
H_2O Na^+
Na^+Cl^-
Na^+Cl^-
H_2O Na^+ Urea
H_2O Na^+ Urea
Concentrated urine
J. Perkins MS, MFA
Max
0
Plasma [ADH]
270
290
310
Plasma osmolality (mOsm/kg H_2O)
Max
0
Plasma [ADH]
−30
−20
−10
0
10
20
% Change in blood volume or pressure

EFFECTS

ADH exerts multiple effects on the kidneys and cardiovascular system, which include the following:

- In collecting ducts, ADH binds to V2 receptors on the basolateral membrane of principal cells, initiating a signaling cascade that leads to apical insertion of aquaporin channels. The collecting duct becomes permeable to water, which is reabsorbed because of the high osmotic pressure generated by the solute concentrated in the medullary interstitium. Over the long term, ADH also increases transcription of aquaporin channels. Nephrogenic diabetes insipidus is a well-characterized condition in which there is dysfunction of ADH-mediated aquaporin insertion (see Plate 3-27).
- ADH increases the reabsorption of sodium and urea, which increases the solute concentration in the medullary interstitium. As a result, there is a larger gradient for water reabsorption. In the thick ascending limb, ADH up-regulates apical NKCC2 $Na^+/K^+/2Cl^-$ cotransporters and ROM-K channels. Over the long term, ADH also increases transcription of NKCC2 cotransporters. In the collecting duct, ADH up-regulates apical ENaC channels and inner medullary urea transporters. As water is reabsorbed in the cortical and outer medullary collecting duct, urea becomes increasingly concentrated in the tubular lumen. Once urea reaches the IMCD, it is reabsorbed along its chemical gradient into the interstitium.
- ADH exerts a pressor effect on vasa recta capillaries, which minimizes the drift of solute away from the medullary interstitium.
- ADH increases peripheral vascular resistance via the V1a receptor, an important effect in volume depletion states. As a result, ADH is a useful pressor hormone in vasodilatory states, such as septic shock. In addition, ADH may be given during cardiac resuscitation.

TUBULOGLOMERULAR FEEDBACK/RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

TUBULAR-GLOMERULAR INTERACTION

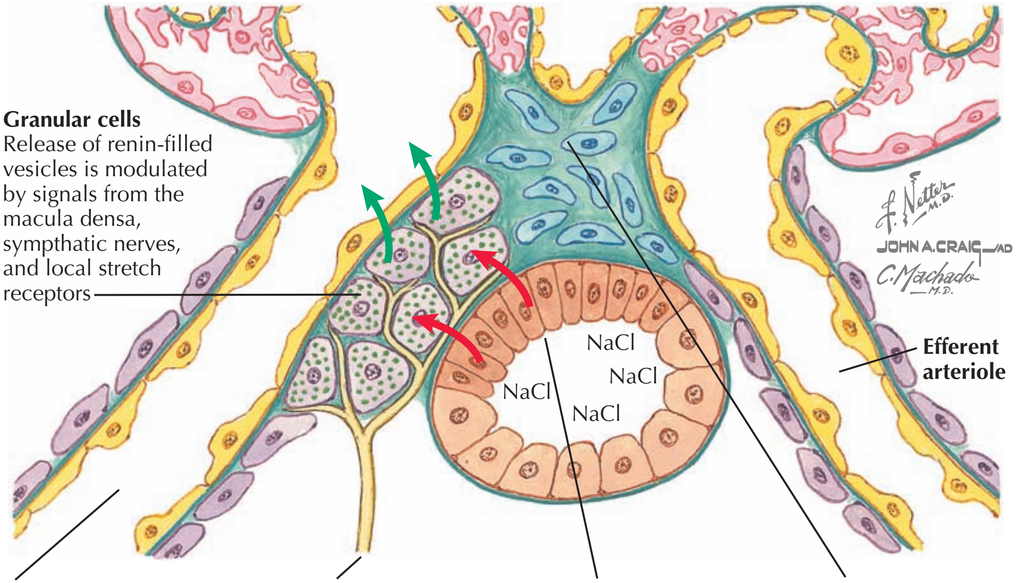
Each tubule communicates with its parent glomerulus as part of a feedback circuit that counteracts the variations in the glomerular filtration rate (GFR) that result from changes in renal perfusion pressure. As a result, the GFR remains nearly constant under a wide range of hemodynamic conditions.

Both the sensor and effector limbs of this feedback circuit reside in the juxtaglomerular apparatus, located where the distal tubule of a nephron contacts its parent glomerulus. As described on Plate 1-20, the juxtaglomerular apparatus contains the macula densa (located in the thick ascending limb), terminal afferent arteriole, initial efferent arteriole, and extraglomerular mesangium. Within this structure, the macula densa acts as the flow rate sensor. When tubular flow rates are decreased, as occurs when the GFR is decreased, the macula densa produces a signal that causes afferent arteriolar vasodilation, restoring the GFR to normal. In contrast, when tubular flow rates are increased, as occurs when the GFR is increased, the macula densa produces a signal that causes afferent arteriolar vasoconstriction, again restoring the GFR to normal.

The interactions between the macula densa and glomerulus also affect activation of the renin-angiotensin-aldosterone system (RAAS). Whereas TGF is designed to control for fluctuations in the single nephron GFR, activation of the RAAS helps address the changes in overall volume status that such fluctuations often imply. When tubular flow rates are reduced, for example, the macula densa triggers renin secretion from granular cells, which are located in the walls of the terminal afferent arteriole and initial efferent arteriole. Renin release has multiple effects, described later in detail, that promote volume retention and systemic vasoconstriction. When flow rates are increased, renin secretion is suppressed.

In addition to signals from the macula densa, several additional factors can also modulate both afferent arteriolar tone and renin release. A rise in renal perfusion pressure, for example, causes stretching of the afferent arteriole, which increases calcium influx into smooth muscle and granular cells. The result is afferent arteriolar vasoconstriction, which preserves the local GFR, as well as suppression of renin release. Meanwhile, increased sympathetic tone, as occurs during volume depletion, leads to afferent arteriolar vasoconstriction, which redirects blood toward organs with high oxygen extraction (brain, heart, skeletal muscle), as well as activation of renin release.

TUBULOGLOMERULAR FEEDBACK AND MODULATION OF RENIN RELEASE



Granular cells
Release of renin-filled vesicles is modulated by signals from the macula densa, sympthatic nerves, and local stretch receptors

Efferent arteriole

Afferent arteriole
Activation of local stretch receptors promotes constriction. Input from macula densa and sympathetic nerves also affect tone.

Sympathetic nerves
Stimulate afferent arteriolar constriction and release of renin-filled vesicles from granular cells

Macula densa
Increased Na^+/Cl^- reabsorption stimulates afferent arteriolar constriction and suppresses renin release from granular cells. Diminished reabsorption stimulates afferent arteriolar vasodilation and promotes renin release.

Extraglomerular mesangial cells
(polkissen, Lacis cells)
Likely act as signaling intermediaries between the macula densa and granular cells

Stimulus	Effect
Increased tubular flow	Afferent arteriolar constriction Suppression of renin release
Decreased tubular flow	Afferent arteriolar dilation Activation of renin release
Afferent arteriole stretching	Afferent arteriolar constriction Suppression of renin release
Sympathetic tone	Afferent arteriolar constriction Activation of renin release

MECHANISMS OF TUBULOGLOMERULAR FEEDBACK

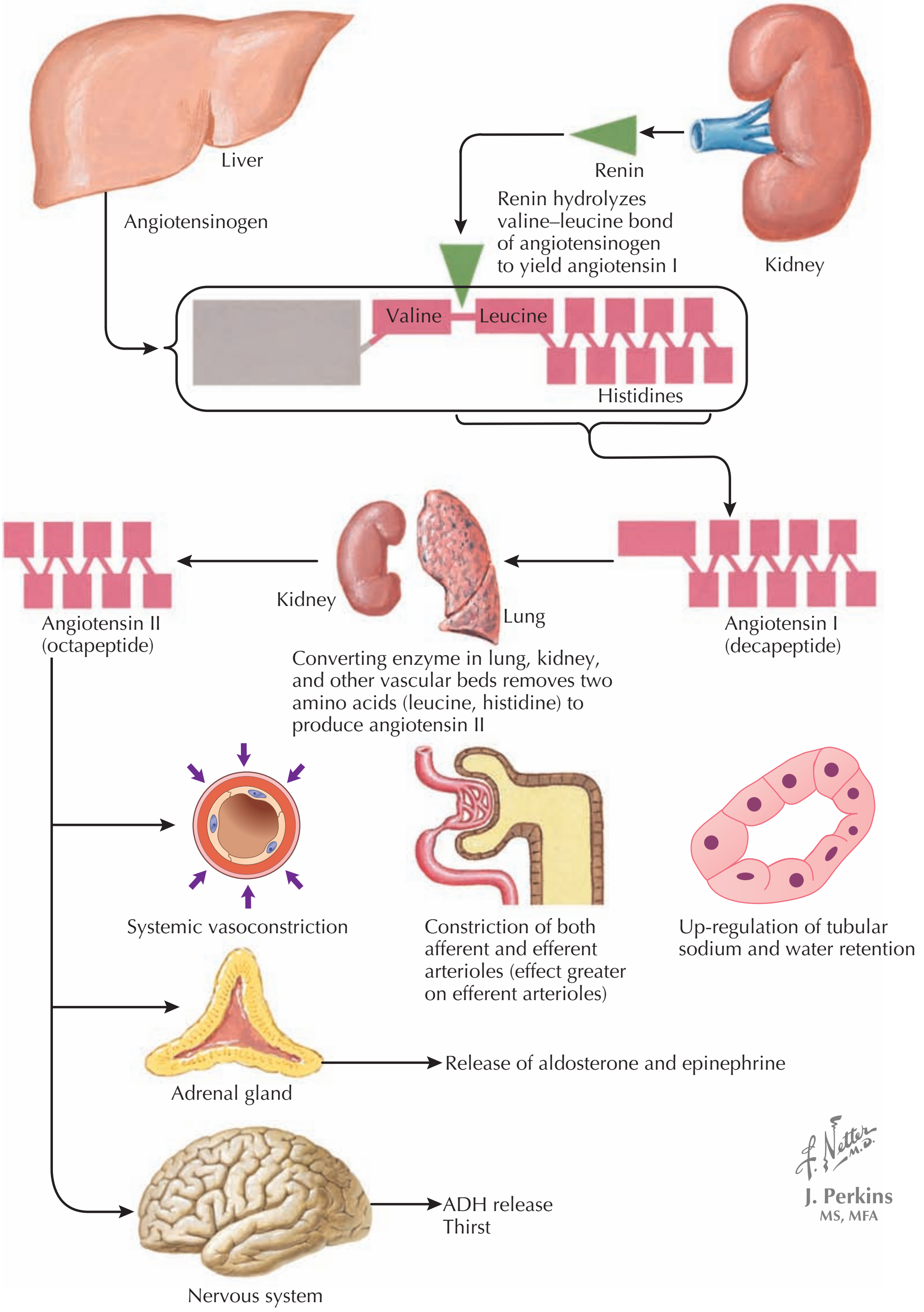
The available evidence suggests that the macula densa, located at the end of the thick ascending limb, senses tubular flow based on the concentrations of sodium and chloride in the local filtrate. The sensing apparatus appears to be apical $Na^+/K^+/2Cl^-$ (NKCC2) cotransporters. When tubular flow rates are high, there is a slight decrease in solute reabsorption before the macula densa, and thus higher concentrations of sodium and chloride are present at this area. Increased activation of NKCC2 transporters ensues, which leads to constriction of the afferent arteriole and inhibition of renin release. In contrast, when tubular flow rates are low, decreased activation of NKCC2 transporters leads to dilation of the afferent arteriole and activation of renin release.

The exact signals that connect the NKCC2 transporters of the macula densa to the afferent and efferent arterioles remain poorly understood; however, there is increasing evidence that adenosine plays a key role. In one proposed model, increased reabsorption by NKCC2 transporters stimulates basolateral Na^+/K^+ ATPases. The increased ATP consumption yields ADP and AMP, which local proteins convert into adenosine. Adenosine, in turn, activates receptors on the surface of nearby extraglomerular mesangial cells, causing an increase in intracellular calcium levels. A wave of intracellular calcium is transmitted across gap junctions to the smooth muscle and granular cells of the afferent and efferent arterioles, causing constriction of the afferent arteriole and inhibition of renin release. In contrast, when there is low tubular flow and diminished reabsorption by NKCC2 transporters, the adenosine signal is eliminated, leading to dilation of the afferent arteriole and stimulation of renin release.

In addition, there is some evidence that macula densa cells contain COX-2 enzymes that are also stimulated when there is diminished reabsorption by NKCC2 transporters; these appear to synthesize prostaglandins that stimulate dilation of the afferent arteriole and promote renin release.

TUBULOGLOMERULAR FEEDBACK/RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM *(Continued)*

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM


Liver
Angiotensinogen
Renin
Renin hydrolyzes valine–leucine bond of angiotensinogen to yield angiotensin I
Kidney
Valine
Leucine
Histidines
Angiotensin II (octapeptide)
Kidney
Lung
Angiotensin I (decapeptide)
Converting enzyme in lung, kidney, and other vascular beds removes two amino acids (leucine, histidine) to produce angiotensin II
Systemic vasoconstriction
Constriction of both afferent and efferent arterioles (effect greater on efferent arterioles)
Up-regulation of tubular sodium and water retention
Adrenal gland
Release of aldosterone and epinephrine
Nervous system
ADH release
Thirst
F. Netter M.D.
J. Perkins
MS, MFA

These mechanisms explain the likely role of TGF in several pathologic conditions. In acute tubular necrosis, for example, there is damage to the proximal tubule, which increases the electrolyte load delivered to the macula densa. As a result, there is severe afferent arteriolar constriction, which is likely a major cause of the decreased filtration function that accompanies this condition. In the early stages of diabetic nephropathy (see Plate 4-46), chronic glucosuria leads to increased glucose-mediated proximal tubular reabsorption, which decreases the electrolyte load delivered to the macula densa. As a result, there is afferent arteriolar vasodilation, leading to hyperfiltration.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Once renin is released it cleaves angiotensinogen (produced in the liver) to angiotensin I. Angiotensin converting enzyme (ACE) then rapidly converts angiotensin I to angiotensin II (AII). ACE is primarily located in pulmonary capillaries but has also been identified elsewhere, including on glomerular endothelial cells. AII, in turn, promotes the release of aldosterone.

Because this hormonal network is activated in response to renal hypoperfusion, its effects raise systemic blood pressure through expansion of extracellular volume and systemic vasoconstriction.

AII has multiple effects. First, it exerts a direct pressor effect on the systemic vasculature. Second, it constricts the efferent (and, to a far lesser extent, afferent) artery, which reduces renal plasma flow without affecting the GFR (see Plate 3-3). These changes thus reduce the fraction of the cardiac output required for normal renal function. They also promote increased reabsorption from the proximal tubule, since the increase in filtration fraction yields greater osmotic pressure and lower hydrostatic pressure in the peritubular capillaries.

In addition to these hemodynamic effects, AII directly promotes sodium and fluid reabsorption from the tubules by up-regulating transporters such as apical NHE-3 Na$^+$/H$^+$ exchangers and basolateral Na$^+$/K$^+$ ATPases in the proximal tubule, as well as apical epithelial sodium channels (ENaC) in principal cells of the collecting duct.

AII also stimulates the production of other hormones and vasoactive substances. For example, just as prostaglandins may play a role in stimulating renin release, AII appears to stimulate production of vasodilatory prostaglandins, such as PGE-2, in the afferent arteriole. This effect may enhance TGF-related vasodilation of the afferent arteriole, and it may partially explain AII's selective vasoconstrictor effect on the efferent arteriole. The interactions between prostaglandins and AII likely explain the precipitous decline in the GFR that may be seen in volume-depleted patients who receive ACE inhibitors or nonsteroidal antiinflammatory drugs. In such patients, blockade of AII or prostaglandin production may interfere with the afferent arteriolar vasodilation required for maintenance of an adequate GFR.

AII also acts at the subfornical organ in the brain, located outside the blood-brain barrier, to promote the release of ADH (see Plate 3-17) and to stimulate thirst. Moreover, it acts on the adrenal medulla to promote catecholamine release.

Finally, AII also stimulates the release of aldosterone, as mentioned above. The major renal effect of aldosterone is to up-regulate apical ENaC and basolateral Na$^+$/K$^+$ ATPases in principal cells of the connecting tubule and collecting duct. The result is an increase in sodium reabsorption, which increases the negative charge in the tubular lumen that promotes secretion of potassium. In addition, aldosterone increases synthesis and apical insertion of the NCC Na$^+$/Cl$^-$ cotransporter in the distal convoluted tubule, further promoting reabsorption of sodium and chloride. Finally, aldosterone also up-regulates apical H$^+$ ATPases in type A intercalated cells of the collecting duct, which promotes acid secretion through the mechanisms described in the pages that follow.

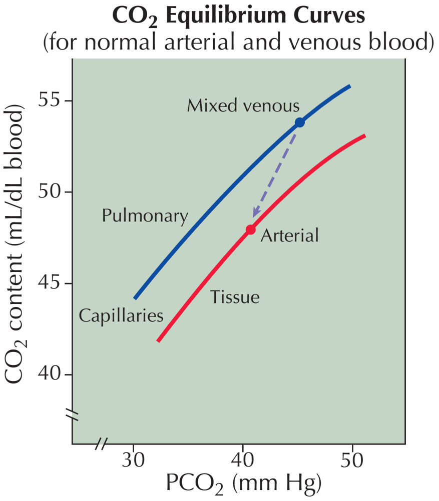
In recent years, AII has been recognized to have many additional effects that are still in the process of being characterized. In the heart, for example, AII appears to promote myocyte hypertrophy and fibroblast proliferation, which contribute to the adverse cardiac remodeling that occurs in the setting of systolic dysfunction. Likewise, in the kidney, AII appears to promote inflammation and extracellular matrix production, contributing to the progressive glomerulosclerosis seen in chronic kidney disease. Because of these effects, ACE inhibitors are becoming the standard of care in all patients with heart failure or chronic kidney disease.

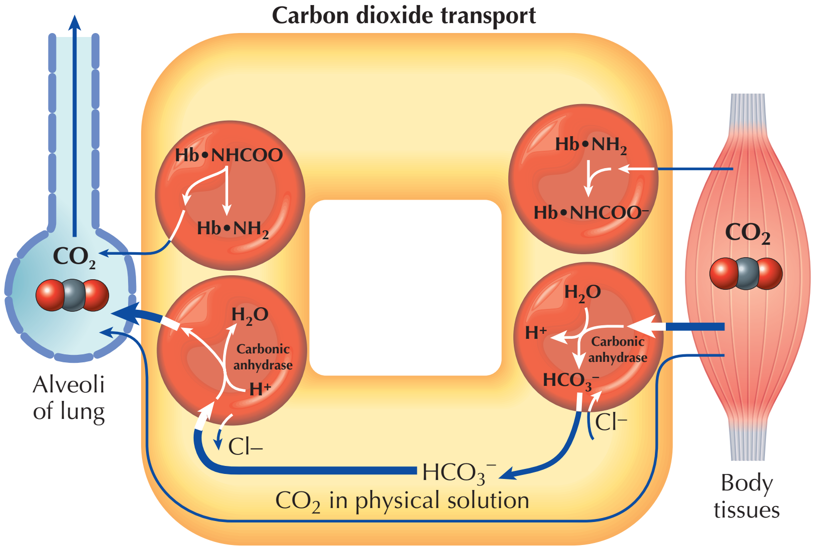
ROLES OF CHEMICAL BUFFERS, LUNGS, AND KIDNEYS IN ACID-BASE HANDLING

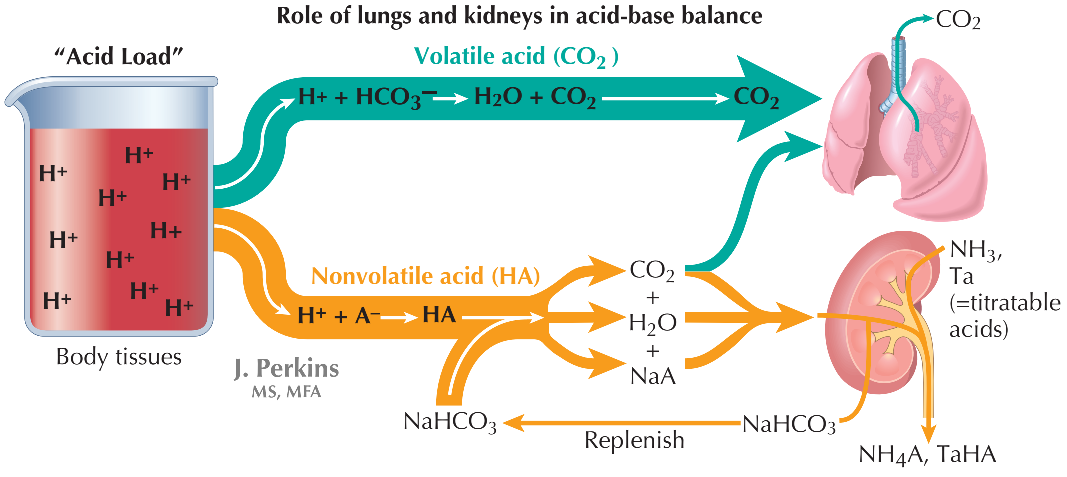
Metabolic production of acid and alkali

Food Source	Acid/Alkali	Quantity (mEq/day)
Carbohydrate Fat	CO_2	15 - 20,000
Amino acids		
S-containing	H_2SO_4	100 (acid)
Cationic	HCl	
Anionic	HCO_3^-	
Organic ions	HCO_3^-	60 (alkali)
Phosphate	$H_2PO_4^-$	30 (acid)
Total		**70 (acid)**

1 mEq/kg/day of nonvolatile acid production


CO_2 Equilibrium Curves
(for normal arterial and venous blood)


Carbon dioxide transport


Role of lungs and kidneys in acid-base balance

ACID-BASE BALANCE

The average human diet contains a significant acid load, but blood pH nonetheless remains within a narrow range (7.36 to 7.44) under normal conditions. Such homeostasis is crucial for normal cellular function, and it reflects the coordinated actions of extracellular and intracellular chemical buffers, the lungs, and the kidneys. Dysfunction of these systems can lead to acidosis or alkalosis, either respiratory or metabolic.

CHEMICAL BUFFERS AND THE LUNGS

The aerobic metabolism of carbohydrates and fats yields a significant load of carbon dioxide. Although carbon dioxide is itself not an acid, it rapidly combines with water to form carbonic acid, which dissociates into a proton and bicarbonate ion. This reaction is catalyzed by carbonic anhydrase, a zinc metalloenzyme found in both the intracellular and extracellular spaces, as follows:

$$CO_{2(\text{dissolved})} + H_2O \overset{\text{Carbonic anhydrase}}{\rightleftharpoons} H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

In this manner, the constant generation of carbon dioxide could lead to a significant acid load. Because carbon dioxide is a volatile gas, however, it can be excreted from the lung, which minimizes its impact. From the peripheral tissues, CO_2 can reach the lung in multiple different manners. First, it may simply be dissolved in plasma. Second, it can enter erythrocytes and become bound to hemoglobin. Finally, and most importantly, it can enter erythrocytes and be converted by carbonic anhydrase into a proton, which is buffered within the cell by hemoglobin, and bicarbonate, which is secreted into the plasma in exchange for chloride.

The metabolism of proteins, in contrast, generates nonvolatile sulfur- and phosphate-based acids, which cannot be directly excreted from the lungs. To neutralize such acids, the extracellular fluid contains buffers that can bind or release protons as needed, so as to minimize fluctuations in the overall proton concentration. The most important extracellular buffer is bicarbonate (HCO_3^-), which can receive a free proton and be converted back into water and carbon dioxide, which is then excreted from the lungs. The ventilation rate is centrally modulated in response to fluctuations in arterial pH so that as more protons are added to the blood, more carbon dioxide is eliminated from the lungs.

The effect of this system can be demonstrated as follows. Because carbonic acid is unstable, the above equation can be simplified as follows:

$$CO_{2(\text{dissolved})} + H_2O \rightleftharpoons HCO_3^- + H^+$$

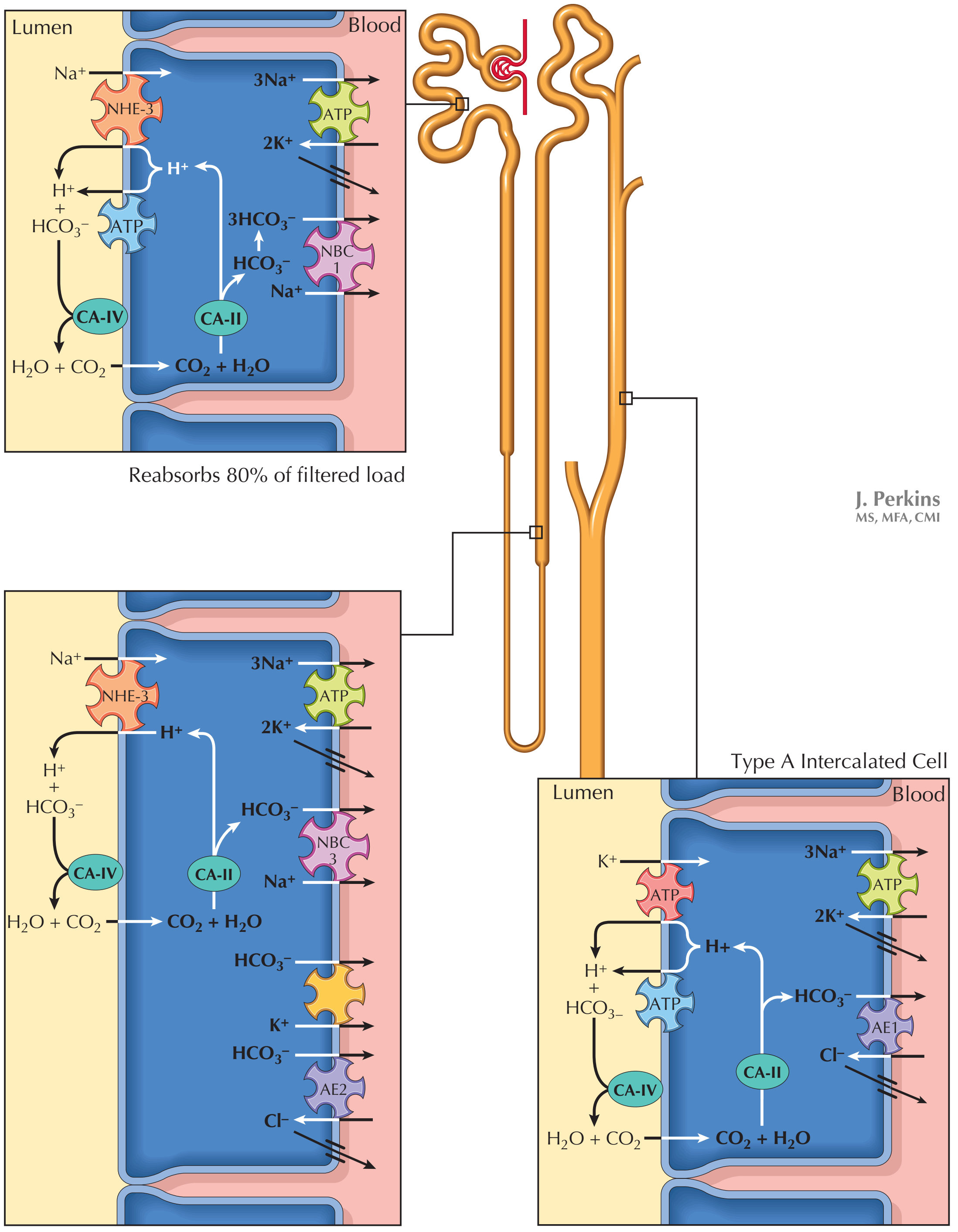
The equilibrium constant, K_a, is equal to:

$$K_a = \frac{[HCO_3^-] \times [H^+]}{[CO_{2(\text{dissolved})}] \times [H_2O]}$$

If K_a' is defined as $K_a * [H_2O]$, then additional rearrangement gives:

$$[H^+] = \frac{K_a' \times [CO_{2(\text{dissolved})}]}{[HCO_3^-]}$$

ACID-BASE HANDLING: RENAL BICARBONATE REABSORPTION



Reabsorbs 80% of filtered load

Reabsorbs 15% of filtered load

Reabsorbs 5% of filtered load

ACID-BASE BALANCE *(Continued)*

By taking the negative logarithm of the above formula, and recognizing that by convention $-\log [H^+] = pH$ and $-\log [K_a'] = pK_a$,

$$pH = pK_a - \log \frac{[CO_{2(dissolved)}]}{[HCO_3^-]}$$

At normal body temperature, the concentration of dissolved carbon dioxide is equal to 3% of its partial pressure. By substitution, and slight further rearrangement:

$$pH = pK_a + \log \frac{[HCO_3^-]}{0.03 \times pCO_2}$$

This formula, an expression of the general Henderson-Hasselbalch equation, demonstrates that as bicarbonate is depleted and carbon dioxide generated, changes in pH are minimized if the partial pressure of carbon dioxide is kept constant or even lowered. Thus, in normal circumstances, the respiratory rate is adjusted so that P_{CO_2} remains constant at about 40 mm Hg.

For this system to remain sustainable, however, a new supply of free bicarbonate ions must be created to replenish the depleted extracellular buffers. Such an event occurs in the renal tubules, where free bicarbonate ions are generated and their paired protons excreted.

KIDNEYS

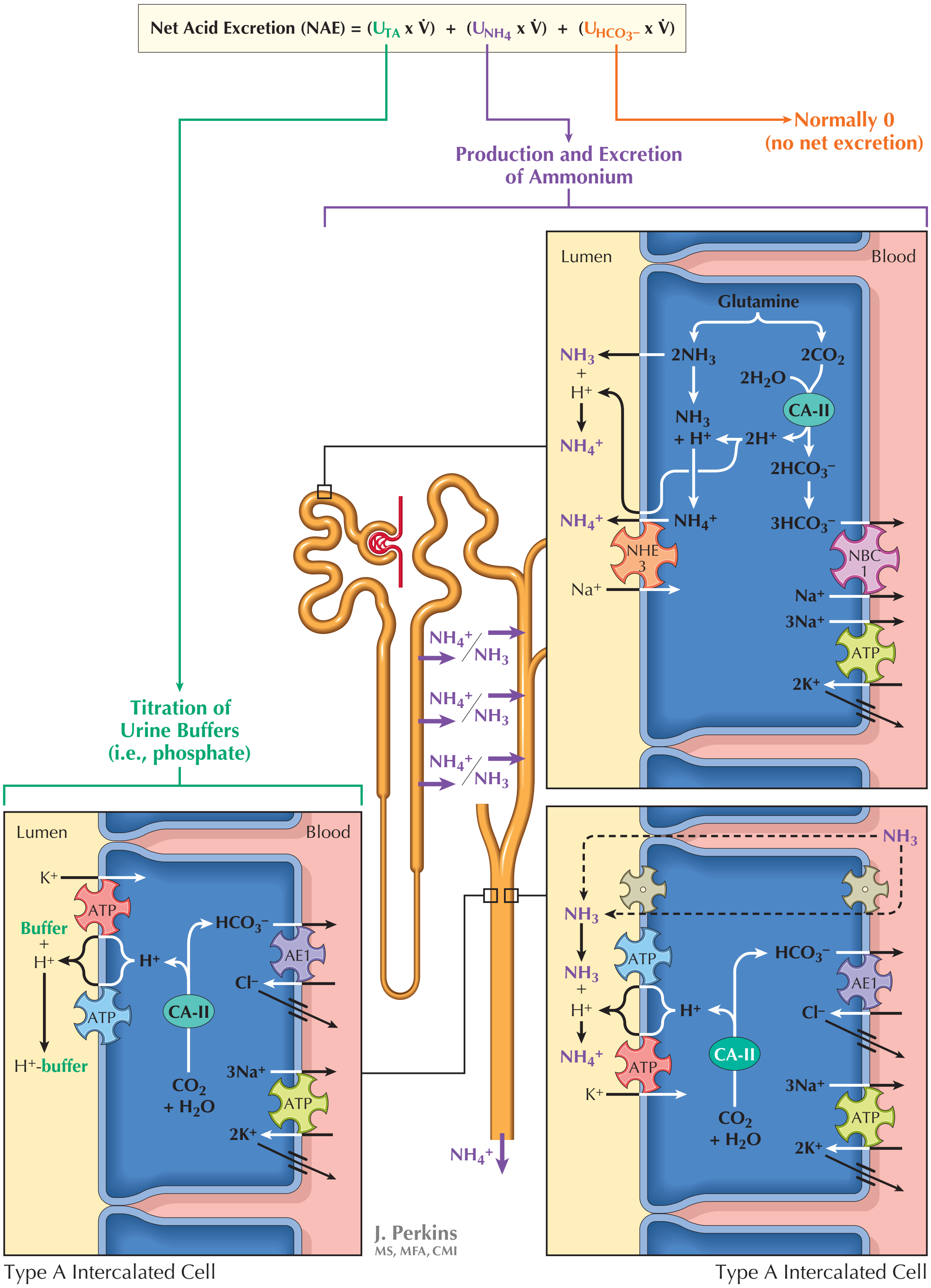
The kidneys are responsible both for reabsorbing existing bicarbonate ions and for generating new bicarbonate ions. The latter process is, by necessity, paired with the excretion of protons, since otherwise the newly generated bicarbonate would simply be converted back into carbon dioxide.

Bicarbonate Reabsorption. Bicarbonate is freely filtered at the glomerulus. About 80% of the filtered load is reabsorbed in the proximal tubule. The process begins in the cytoplasm of the tubular epithelium, where carbonic anhydrase II catalyzes the conversion of carbon dioxide and water into bicarbonate ions and protons. The bicarbonate ions are reabsorbed into the interstitium on basolateral NBC-1 Na^+/HCO_3^- cotransporters; the protons, meanwhile, are secreted across the apical surface on NHE-3 Na^+/H^+ exchangers and, to a lesser extent, H^+ ATPases. Once the protons are in the tubular fluid, membrane-bound carbonic anhydrase IV catalyzes their reaction with filtered bicarbonate ions to produce carbon dioxide and water. The newly formed carbon dioxide diffuses into proximal tubule cells, and the entire process begins again. Note that there is no net proton secretion during this process because protons are recycled across the apical membrane to capture filtered bicarbonate.

About 15% of the filtered bicarbonate load is reabsorbed in the thick ascending limb. The process in this segment is comparable to that seen in the proximal tubule; however, there does not appear to be a significant role for apical H^+ pumps, the basolateral NBC transporter is of a different isoform, and the basolateral membrane also features Cl^-/HCO_3^- exchangers (AE2) and K^+/HCO_3^- symporters.

Nearly all of the remaining bicarbonate is reabsorbed in the collecting duct. Type A intercalated cells are

ACID-BASE HANDLING: RENAL BICARBONATE SYNTHESIS AND PROTON EXCRETION


Net Acid Excretion (NAE) = (U_{TA} x $\dot{V}$) + (U_{NH_4} x $\dot{V}$) + ($U_{HCO_3^-}$ x $\dot{V}$)
Normally 0
(no net excretion)
Production and Excretion of Ammonium
Titration of Urine Buffers (i.e., phosphate)
Lumen
Blood
Glutamine
NH_3
+
H^+
NH_4^+
$2NH_3$
$2CO_2$
$2H_2O$
CA-II
NH_3 + H^+
$2H^+$
$2HCO_3^-$
NH_4^+
$3HCO_3^-$
NHE 3
NBC 1
Na^+
$3Na^+$
ATP
$2K^+$
NH_4^+/NH_3
NH_4^+/NH_3
NH_4^+/NH_3
NH_4^+
Lumen
Blood
K^+
ATP
Buffer
+
H^+
H^+
HCO_3^-
AE1
Cl^-
CA-II
ATP
H^+-buffer
CO_2 + H_2O
$3Na^+$
ATP
$2K^+$
NH_3
NH_3
NH_3
+
H^+
NH_4^+
K^+
ATP
ATP
H^+
HCO_3^-
AE1
Cl^-
CA-II
CO_2 + H_2O
$3Na^+$
ATP
$2K^+$
J. Perkins MS, MFA, CMI
Type A Intercalated Cell
Type A Intercalated Cell

ACID-BASE BALANCE *(Continued)*

responsible for this process. Like the cells in earlier segments, they possess cytoplasmic carbonic anhydrase II, which converts carbon dioxide and water to bicarbonate ions and protons. The protons, however, are secreted in an Na-independent manner using H^+ ATPases and H^+/K^+ ATPases, while the bicarbonate is reabsorbed on Cl^-/HCO_3^- exchangers (AE1, also known as band 3 protein).

Fluctuations in acid-base status directly affect the rate of bicarbonate reabsorption. In the presence of an increased acid load, for example, proximal tubular cells experience an increased intracellular proton concentration, which stimulates NHE-3 cotransport via direct pharmacokinetics and an allosteric effect. Likewise, increased CO_2 concentration stimulates insertion of vesicles containing NHE-3 transporters and H^+ ATPases into the proximal tubular apical cell membrane.

Several hormones also modulate the rate of bicarbonate reabsorption. Cortisol and endothelin-1, for example, are released in response to acidosis and increased bicarbonate reabsorption in the proximal tubule. Angiotensin II, released in response to hypovolemia, also increases bicarbonate reabsorption in the proximal tubule, where it upregulates the apical NHE-3 exchanger.

Although under normal circumstances bicarbonate reabsorption is complete, under certain conditions there is active secretion of bicarbonate into the cortical collecting duct. Type B intercalated cells are responsible for this process; they possess pendrin, an HCO_3^-/Cl^- exchanger, on their apical surface and an H^+ ATPase on their basolateral surface.

Bicarbonate Synthesis / Proton Excretion. As mentioned above, synthesis of new bicarbonate ions must be coupled with net excretion of protons. The apical proton pumps, however, can only tolerate a 1000:1 transepithelial proton gradient, which is equivalent to a minimum urine pH of 4.4 (given a normal plasma pH of 7.4). To circumvent this limitation, protons are buffered in urine by titratable acids or excreted as ammonium.

Titratable Acids. Urine contains several weak acids that serve as urinary buffers. These buffers are also called "titratable acids" because their concentration can be determined based on how much NaOH is required to titrate collected urine to a pH of 7.4.

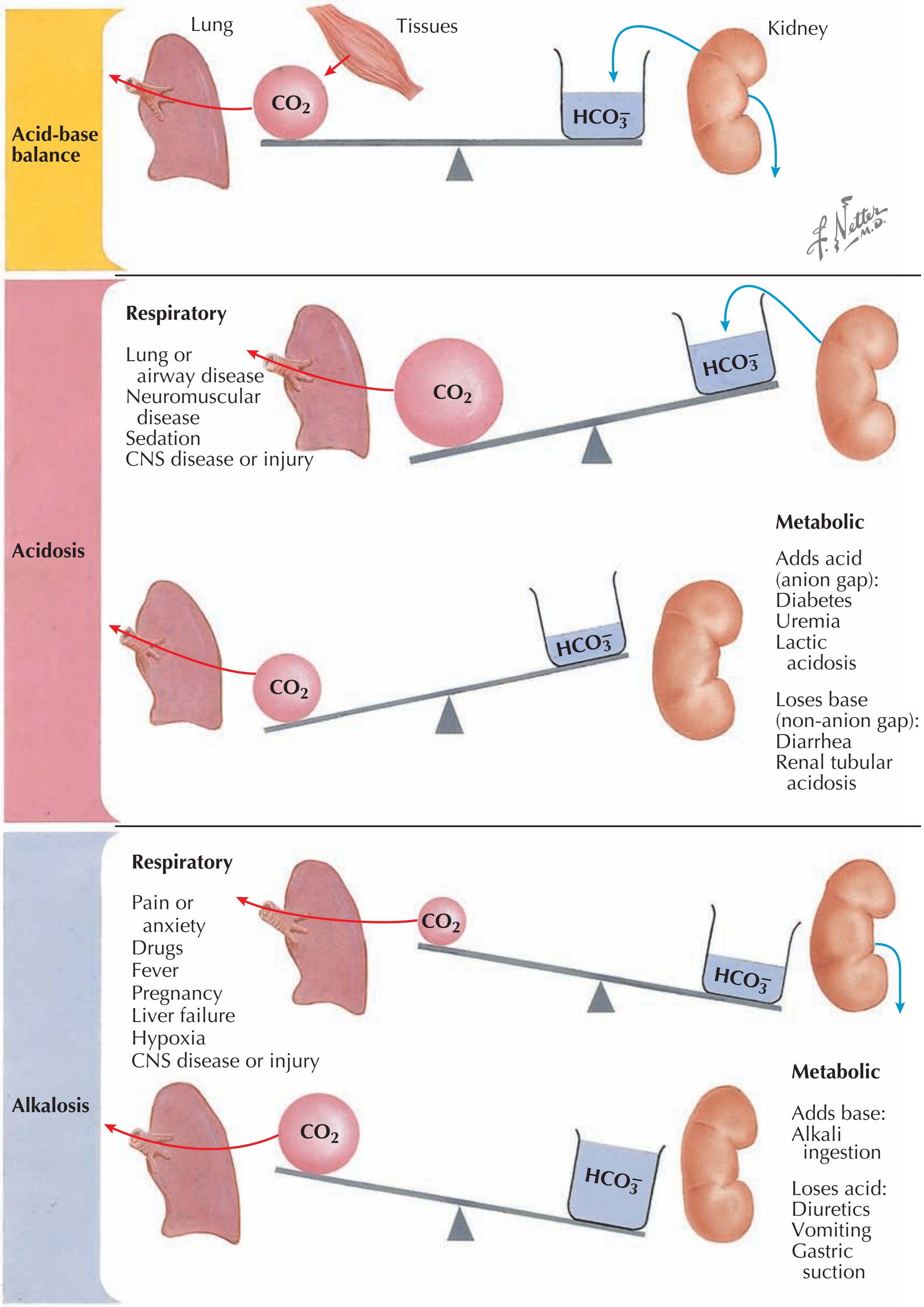
Phosphate, which exists in plasma primarily as HPO_4^{2-}, is the major titratable acid in urine because its pKa of 6.8 is near physiologic pH. Using the Henderson-Hasselbalch equation, the ratio of protonated to unprotonated species can be expressed as follows:

$$pH = 6.8 + \log\frac{[HPO_4^{2-}]}{[H_2PO_4^{-}]}$$

At a pH of 7.4, the ratio of HPO_4^{2-} to $H_2PO_4^-$ is 4:1 based on the above equation. Thus, four fifths of the filtered phosphate is available to buffer protons.

Most of the $H_2PO_4^-$ is protonated in the collecting duct. As described previously, type A intercalated cells possess cytoplasmic carbonic anhydrase II, which converts carbon dioxide and water to bicarbonate ions, which are reabsorbed, and protons, which are secreted. Some of the secreted protons contribute to bicarbonate reabsorption, as described previously, but most combine with buffers such as HPO_4^{2-}. The overall process leads to net synthesis of bicarbonate ions and excretion of protons.

ACIDOSIS AND ALKALOSIS


Acid-base balance
Lung
Tissues
Kidney
CO_2
HCO_3^-
F. Netter M.D.
Acidosis
Respiratory
Lung or airway disease
Neuromuscular disease
Sedation
CNS disease or injury
CO_2
HCO_3^-
Metabolic
Adds acid (anion gap):
Diabetes
Uremia
Lactic acidosis
Loses base (non-anion gap):
Diarrhea
Renal tubular acidosis
CO_2
HCO_3^-
Alkalosis
Respiratory
Pain or anxiety
Drugs
Fever
Pregnancy
Liver failure
Hypoxia
CNS disease or injury
CO_2
HCO_3^-
Metabolic
Adds base:
Alkali ingestion
Loses acid:
Diuretics
Vomiting
Gastric suction
CO_2
HCO_3^-

ACID-BASE BALANCE *(Continued)*

Several factors can stimulate proton secretion in the collecting duct. In the setting of acidosis, subapical vesicles containing additional H^+ ATPases fuse with the apical plasma membrane of type A intercalated cells. If acidosis is chronic, type A intercalated cells become hypertrophic, further increasing their acid-secreting capabilities. Increased delivery of sodium to the collecting duct results in greater reabsorption through ENaC, resulting in a more negative intraluminal charge that promotes the secretion of protons, just as it promotes the secretion of potassium. Aldosterone also stimulates proton secretion through several mechanisms. First, it stimulates sodium reabsorption through ENaC, which results in a strong negative charge in the collecting duct lumen that increases the gradient for proton secretion. Second, it has a direct stimulatory effect on H^+ ATPases. Finally, hypokalemia also stimulates proton secretion through up-regulation of H^+/K^+ ATPases, as well as through stimulating basolateral efflux of potassium in exchange for protons, which increases the intracellular proton concentration and thus the gradient for proton secretion.

Ammonium. In proximal tubular cells, the metabolism of glutamine offers another mechanism for synthesizing new bicarbonate ions and excreting protons. The metabolism of each molecule of glutamine yields two ammonia (NH_3) ions, one during the conversion to glutamate (by glutaminase), and another during the conversion to α-ketoglutarate (by glutamate dehydrogenase). α-Ketoglutarate yields two carbon dioxide molecules as it passes through the citric acid cycle.

The carbon dioxide molecules combine with water to form bicarbonate ions, which are reabsorbed, and protons. The protons rapidly combine with the newly synthesized NH_3 to form ammonium (NH_4^+), a reaction that can occur either in the cytoplasm or tubular lumen. In the former case, NH_4^+ is secreted into the lumen of the NHE-3 exchanger. In the latter case, the protons are secreted into the lumen on the NHE-3 exchanger, and the hydrophobic NH_3 freely diffuses across the apical plasma membrane.

The NH_4^+ in the tubular lumen exists in dynamic equilibrium with NH_3. As a result, NH_3 can freely diffuse back into the interstitium. If this NH_3 were not reclaimed, the free protons left in the tubular lumen would rapidly deplete titratable acid buffers. Therefore, to ensure that any lost NH_3 reenters the tubular lumen, NH_4^+ is reabsorbed across the cells of the thick ascending limb (e.g., on the K^+ position of the NKCC2 cotransporter), deprotonated, and released as NH_3 into the interstitium. Although this mechanism seems counterproductive, it creates a high concentration of NH_3 in the medullary interstitium, which favors its diffusion back into the collecting duct. Such diffusion is enhanced by the presence of NH_3 transporters, such as Rhcg, on the basolateral and apical surfaces of type A intercalated cells. Once NH_3 enters the collecting duct lumen, it is reprotonated and finally excreted.

Acidosis directly up-regulates ammoniagenesis through various mechanisms. Hypokalemia also up-regulates ammoniagenesis, whereas hyperkalemia down-regulates it, likely because of the effects of basolateral H^+/K^+ exchange on intracellular pH. Angiotensin II also up-regulates ammoniagenesis by stimulating the NHE-3 exchanger, which increases NH_4^+ secretion. Meanwhile, several factors increase proton secretion in the collecting duct, as described in the section on titratable acids.

ADDITIONAL FUNCTIONS: ERYTHROPOIESIS AND VITAMIN D

ERYTHROPOIESIS

Red blood cells must be plentiful enough to ensure adequate oxygenation of peripheral tissues, yet not so numerous as to compromise the free flow of blood. Therefore, erythropoiesis must be under tight control. The kidneys play an essential role in this process because they sense hypoxia, the major sign of inadequate erythrocyte mass, and respond by secreting erythropoietin, the major promoter of erythrocyte production.

The oxygen-sensitive production of erythropoietin occurs in peritubular fibroblasts. These cells are responsible for constitutive production of hypoxia-inducible factor 1 (HIF-1), a heterodimeric protein with α and β subunits.

In the setting of high oxygen tension, the α subunit undergoes rapid hydroxylation by proline hydroxylases (PHDs). The hydroxylated α subunit then combines with the von Hippel-Lindau tumor suppressor, undergoes ubiquitination, and is degraded in proteasomes.

In contrast, in the setting of hypoxia, the HIF-1 heterodimer persists and combines with various proteins, such as p300 and CBP, to form a transcription factor. This factor binds to the hypoxia-responsive element located near the *EPO* gene and upregulates the synthesis of many proteins, including erythropoietin. In the bone marrow, erythropoietin enhances the survival and maturation of colony-forming units-erythroid (CFU-E), which then give rise to erythrocytes.

Erythropoietin deficiency occurs in advanced renal failure, resulting in the emergence of a significant normocytic anemia. The increasing availability of recombinant erythropoietin agents, however, has all but eliminated the need for transfusion in dialysis patients. Nonetheless, there is a small but significant increased risk of cardiovascular events and death associated with this class of drugs.

VITAMIN D

Vitamin D is a fat-soluble vitamin that can be acquired either from diet or from sunlight-induced conversion of epidermal fats. In either case, vitamin D undergoes numerous modifications in various organs, including the kidneys, to become a bioactive hormone. (For an illustration, see Plate 4-67).

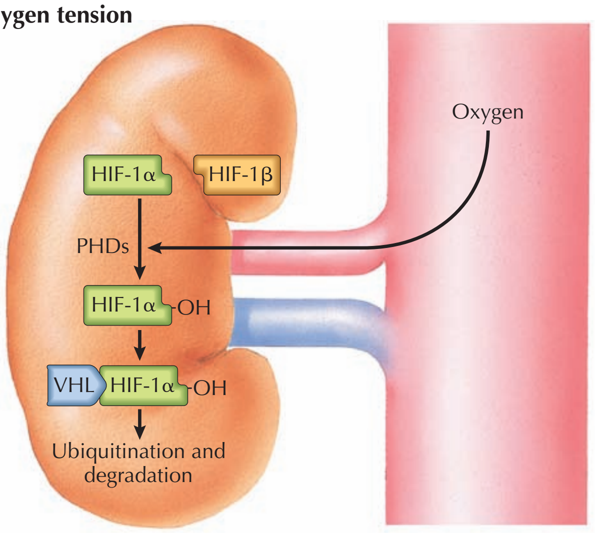
Vitamin D synthesis begins when ultraviolet waves in sunlight cause photoisomerization of 7-dehydrocholesterol to vitamin D_3 (cholecalciferol), or when vitamin D_2 (ergocalciferol) or D_3 is ingested and absorbed. Major dietary sources of vitamin D include fatty fish and fortified milk. Because vitamin D is fat soluble, inadequate absorption occurs in fat malabsorption states, such as pancreatic insufficiency or cystic fibrosis.

Vitamins D_2 and D_3 are carried on plasma vitamin D–binding proteins to the liver, where 25-hydroxylase converts them to 25-hydroxyvitamin D [calcidiol, abbreviated as 25(OH)D]. From there, 25(OH)D eventually reaches the kidneys, again on vitamin D–binding proteins. 25(OH)D enters proximal tubular epithelial cells via receptor-mediated endocytosis, where it is converted by 1-α-hydroxylase to 1,25-dihydroxyvitamin D [calcitriol, the bioactive vitamin, abbreviated as 1,25$(OH)_2$D]. 1-α-hydroxylase is upregulated in the presence of PTH, hypocalcemia, and hypophosphatemia. Another proximal tubular enzyme, known as 24-α-hydroxylase, can synthesize an inactive form of vitamin D known as 24,25-dihydroxyvitamin D. This enzyme is upregulated in the presence of 1,25$(OH)_2$D, which therefore regulates its own synthesis.

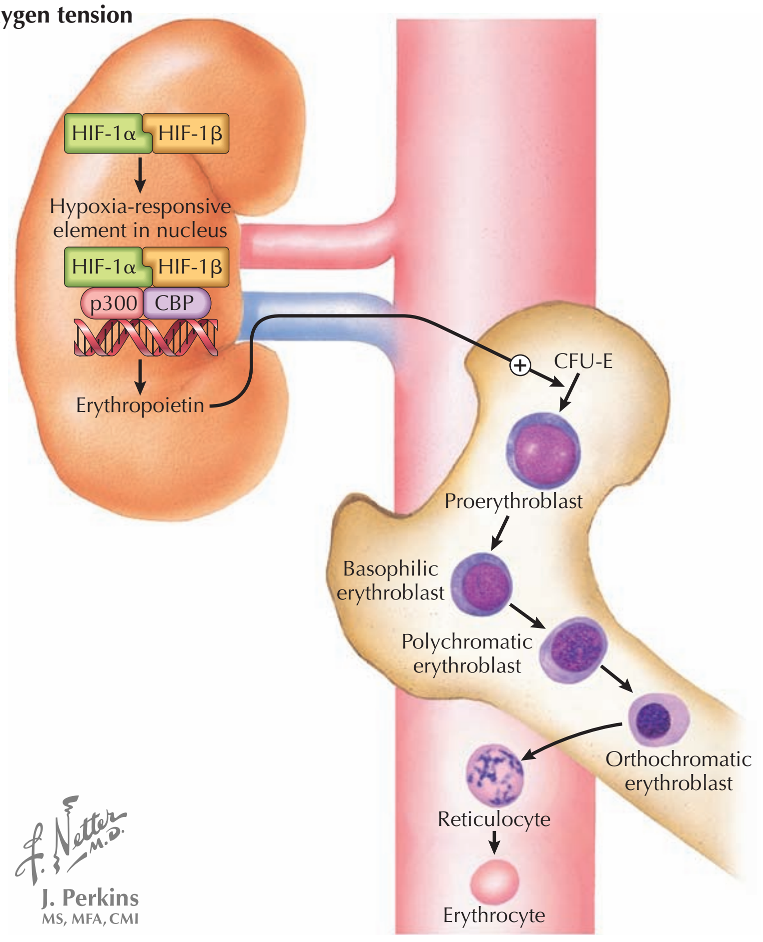
Vitamin D's major functions are to increase the intestinal reabsorption of calcium and phosphate, to stimulate bone metabolism, and to suppress the release of PTH. As a result, profound bone mineralization defects occur in states of deficiency. Such defects are a major component of the phenomenon known as renal osteodystrophy, which occurs in end-stage renal disease (see Plate 4-70).

ROLE OF KIDNEYS IN ERYTHROPOIESIS

High oxygen tension



Low oxygen tension

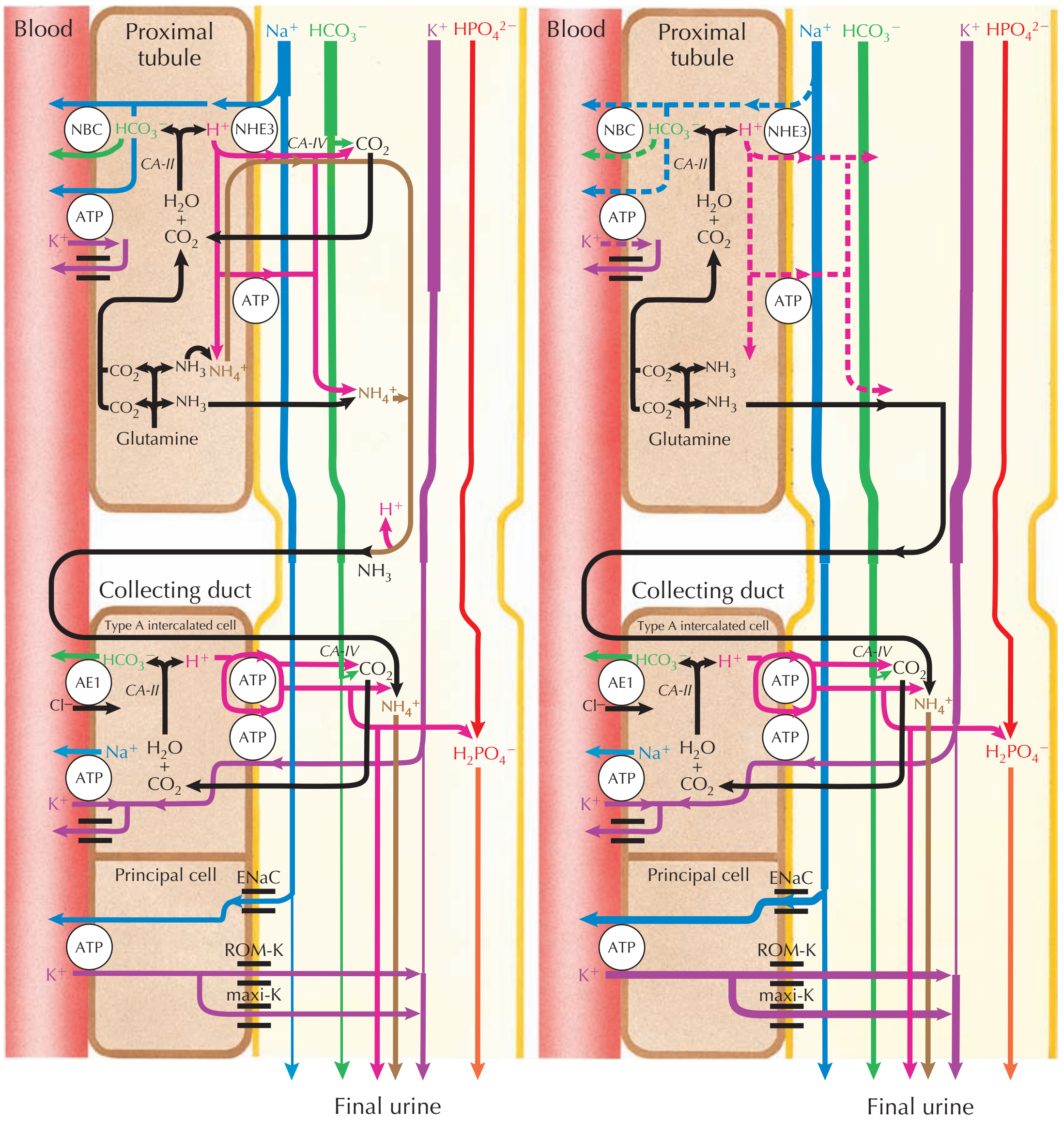


RENAL TUBULAR ACIDOSIS

PROXIMAL RENAL TUBULAR ACIDOSIS

Normal urinary acidification

Proximal renal tubular acidosis



Normally, bicarbonate is extensively reabsorbed in the proximal tubule, and consequently the fractional excretion of bicarbonate is very low.

Proximal RTA causes increased urinary excretion of bicarbonate and potassium. Once serum bicarbonate concentrations are low enough, however, the collecting duct can recapture all of the bicarbonate wasted from the proximal tubule.

In response to a load of bicarbonate salts, however, the kidneys will resume wasting bicarbonate.

With global proximal dysfunction, as shown above, there is also increased urinary excretion of sodium, glucose, amino acids, phosphate, uric acid, albumin.

F. Netter M.D.

The kidneys play a key role in maintaining systemic pH near 7.4. The renal tubular acidoses (RTAs) are a group of disorders in which systemic acidosis occurs because the kidneys are unable either to excrete acid or to conserve bicarbonate. In either case, the result is a variable degree of normal anion gap metabolic acidosis accompanied by an abnormal serum potassium concentration. The RTA subtypes are classified as proximal or distal (pRTA, dRTA) based on which nephron segment is malfunctioning.

PROXIMAL RTA

The proximal tubule reabsorbs 80% of the filtered bicarbonate (see Plate 3-21). Proximal tubular cells also metabolize glutamine, a process that yields bicarbonate, which is reabsorbed, and NH_4^+, which is secreted into the nascent urine.

Proximal RTA (pRTA), in which these processes fail, usually occurs as a component of generalized proximal tubular dysfunction (renal Fanconi syndrome). Most cases are acquired, reflecting exposure to substances that interfere with proximal tubular function, such as myeloma proteins or drugs (e.g., cytotoxic drugs or sodium valproate). In rarer cases, generalized proximal dysfunction may result from inherited diseases, such as cystinosis (see Plate 4-64). In even rarer cases, pRTA may be an isolated phenomenon (i.e., otherwise normal proximal function), as seen in individuals with recessively inherited defects in the basolateral NBC Na^+/HCO_3^- transporter.

Because the distal nephron can recapture some of the bicarbonate that is not reabsorbed in the proximal tubule, pRTA generally features a milder acidosis than dRTA. Indeed, once serum bicarbonate levels decline to 15 mEq/L, reabsorption in the distal nephron can fully compensate for the proximal dysfunction. At this point, bicarbonate wasting ceases, urine pH decreases (often becoming acidic), and serum bicarbonate concentrations stabilize. If patients are given an intravenous infusion of sodium bicarbonate, however, bicarbonate wasting resumes (with a fractional excretion of ≥15%) and the urine pH increases. This sequence of events is diagnostic of proximal RTA.

In addition to acidosis, pRTA features hypokalemia because the nonreabsorbed bicarbonate produces a negative charge in the collecting duct lumen, promoting K^+ secretion through ROM-K channels. If there is generalized proximal tubule dysfunction, the increased distal Na^+ load that reaches the cortical collecting duct also produces a negative intraluminal charge as it is reabsorbed. In addition, the increased urine flow through the distal tubule, which results from proximal salt wasting, stimulates K^+ secretion through flow-sensitive maxi-K channels.

Although acidosis and hypokalemia are the hallmarks of pRTA, several additional abnormalities are often seen. Patients with generalized proximal tubular dysfunction, for example, exhibit salt wasting, polyuria, phosphaturia (and hypophosphatemia), glucosuria, uricosuria (and hypouricemia), aminoaciduria, microalbuminuria, and low molecular weight proteinuria (e.g., retinol binding protein or β_2-microglobulin). Moreover, patients often develop rickets or osteomalacia (depending on age) because of inefficient renal activation of vitamin D. Meanwhile, patients with isolated pRTA, like those with NBC transporter mutations, often have aberrant calcification within the eyes (band keratopathy), cataracts, and mental retardation.

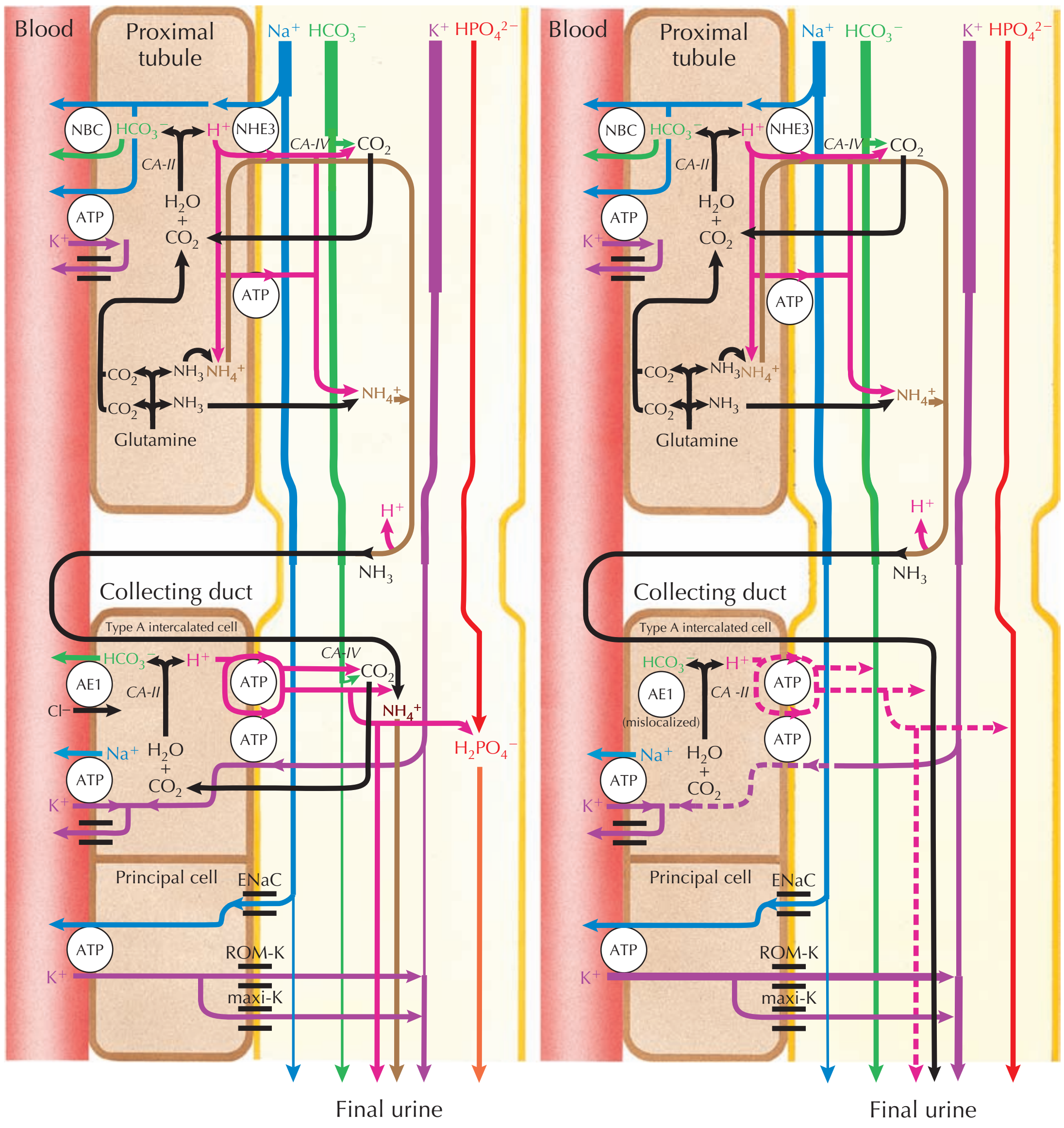
Proximal RTA is often difficult to treat because the marked bicarbonaturia mandates that large quantities of alkali be provided on a regular basis. Extensive bicarbonate supplementation, however, often causes worsening hypokalemia, and thus potassium supplements are often required as well. If there is generalized proximal tubular dysfunction, vitamin D and phosphate supplements are also helpful.

DISTAL RTA

The collecting duct contains principal cells and intercalated cells (ICs), with the latter responsible for acid-base handling. Within the IC population, at least two

RENAL TUBULAR ACIDOSIS

(Continued)



CLASSIC DISTAL RENAL TUBULAR ACIDOSIS

Normal urinary acidification

Distal renal tubular acidosis

Normally, acid is excreted as free protons, ammonia, and titratable acids.

In distal RTA, the lack of proton secretion in the collecting duct prevents protonation of ammonium and titratable acids, as well as excretion of free protons. As a result, urine is inappropriately akaline despite systemic acidosis. In addition, there is increased potassium excretion.

subtypes of cells have been described: type A and type B. Type A cells secrete protons and reabsorb bicarbonate, whereas type B cells do the reverse. It is unclear if type A and B cells are molecular mirror images or separate cell types; however, the acid load in the average human diet dictates that the great majority of ICs be type A.

Classic distal RTA (i.e., hypokalemic dRTA) reflects type A cell dysfunction. Because there is inadequate secretion of protons, the kidneys are unable to appropriately acidify urine in the setting of systemic metabolic acidosis or following an acid load (e.g., with ammonium chloride). The urine anion gap (urine $Na^+ + K^- - Cl^-$) is a useful tool for confirming this defect; it will be positive in patients with metabolic acidosis if there are low levels of urine NH_4^+, the major unmeasured cation, secondary to impaired urine acidification.

In most cases classic dRTA is acquired. Major causes include immunologic diseases (e.g., Sjögren syndrome) and drugs (e.g., lithium, amphotericin). Rarely, classic distal RTA can occur during pregnancy, although it typically resolves after delivery. Genetic causes have also been reported, such as autosomal dominant (and, rarely, autosomal recessive) mutations in the gene encoding AE1, as well as autosomal recessive mutations in subunits of the apical proton pump.

No matter the cause, classic dRTA generally features hypokalemia, at least in part because the lack of proton secretion in the collecting duct increases the gradient for potassium secretion. Nephrolithiasis and/or nephrocalcinosis are also common, since calcium precipitation is favored by urine alkalinity, which results from failure of proton secretion, and hypocitraturia, which results from the increased citrate reabsorption that occurs in response to acidosis. Metabolic bone disease (osteomalacia or rickets) may occur because of the effects of acidosis on bone, even though calcium and phosphate levels are usually normal. In patients with autosomal recessive dRTA, progressive and irreversible bilateral sensorineural hearing loss is common, reflecting the functional significance of the H^+ pump in the cochlea.

Classic dRTA is treated with alkali replacement. If treatment is not instituted early on, however, chronic kidney disease may occur secondary to nephrocalcinosis or uncontrolled nephrolithiasis with consequent obstruction. Of note, alkali treatment does not improve deafness in patients with autosomal recessive disease because orally administered alkali cannot access the inner ear compartment.

Hyperkalemic dRTA is chiefly a by-product of distal nephron dysfunction secondary to aldosterone resistance or deficiency. Acidosis reflects both the absence of aldosterone-induced proton secretion and the inhibitory effects of hyperkalemia on ammoniagenesis.

Most cases are related to drugs or to hyporeninemic hypoaldosteronism. The most commonly implicated drugs include trimethoprim, cyclosporine, and ACE inhibitors. Trimethoprim acts as an antagonist of the ENaC, whereas cyclosporine inhibits the basolateral Na^+/K^+ ATPase. Hyporeninemic hypoaldosteronism is most often found in the context of renal insufficiency, especially that caused by diabetes mellitus.

Hyperkalemic dRTA is treated by withdrawing precipitating drugs and providing sodium bicarbonate. Fludrocortisone and/or potassium-lowering drugs, such as oral resins, are also helpful, since reducing serum potassium concentrations increases renal ammoniagenesis and ammonia excretion.

MIXED RTA

The entity of transient mixed proximal/distal RTA arising just after birth is thought to mark a developmental hiatus in distal nephron function, which normally continues to mature after birth. Nontransient RTA with both proximal and distal tubular dysfunction does, however, accompany one form of autosomal recessive osteopetrosis (Guibaud-Vainsel syndrome or marble brain disease). Investigators have identified loss of carbonic anhydrase 2, an enzyme expressed both throughout the nephron and in osteoclasts, as the biochemical defect. The disease presents in infancy, with major signs including thickened but brittle bones, short stature, mental retardation, dental malocclusion, and visual impairment from optic nerve compression. Calcification of the basal ganglia may occur.

NEPHROGENIC DIABETES INSIPIDUS

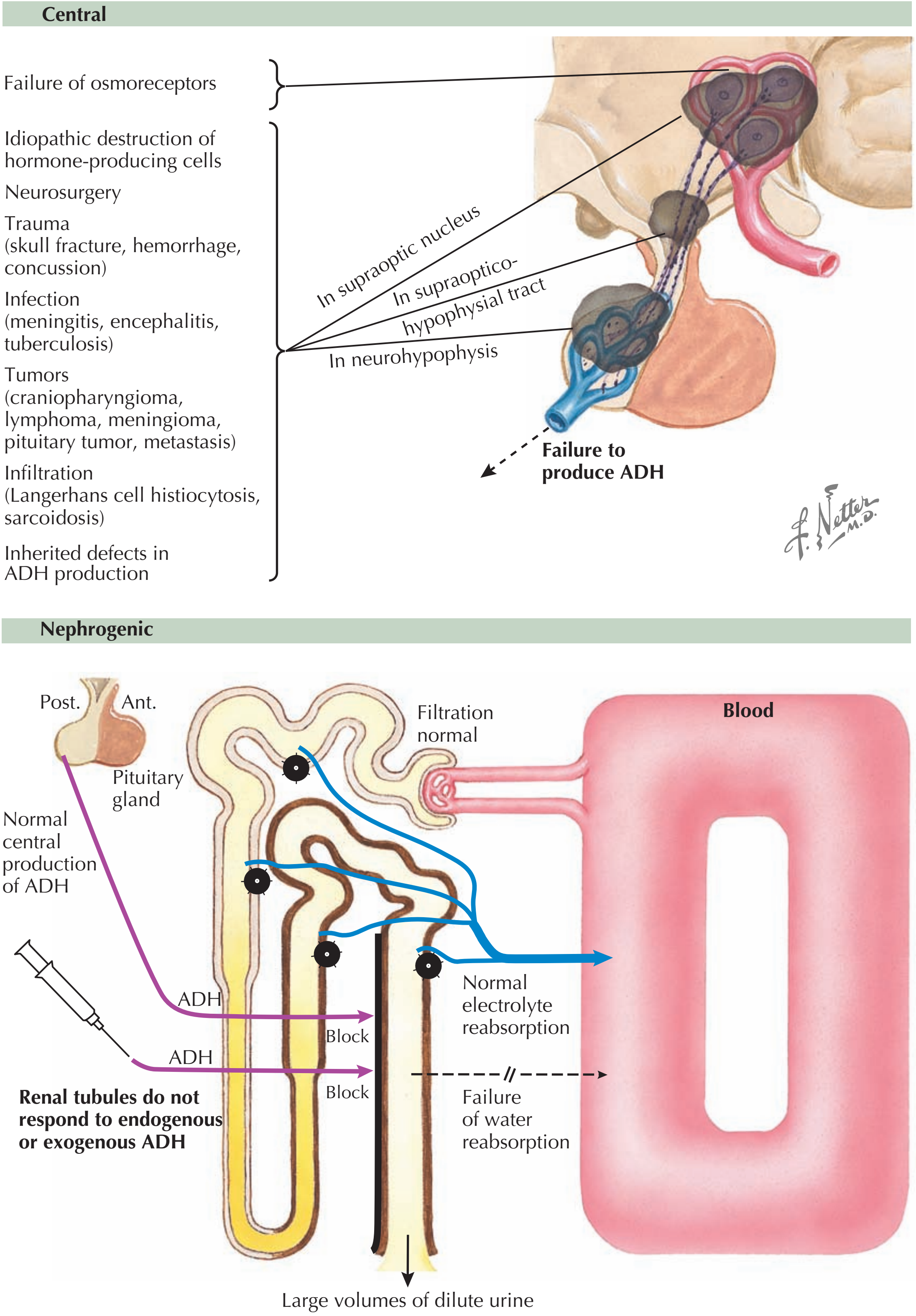
In diabetes insipidus (DI), abnormalities in ADH signaling prevent patients from appropriately concentrating tubular fluid, leading to the continuous production of large volumes of dilute urine. DI is termed “central” if there is diminished production of ADH, usually because of abnormalities in the hypothalamus or posterior pituitary, or “nephrogenic” if there is diminished renal response to ADH. Nephrogenic DI (NDI) can occur because of inherited mutations or, more commonly, acquired insults to the renal tubules.

PATHOPHYSIOLOGY

A detailed description of ADH physiology is available on Plate 3-17. In brief, elevations in serum osmolality trigger release of ADH from the posterior pituitary. In the kidneys, ADH binds to V2 receptors on the basolateral surface of principal cells, located in the collecting duct, which triggers translocation of aquaporin 2 (AQP-2) channels from endosomes to apical cell membranes. As a result, water is reabsorbed through a transcellular route from the tubule lumen into the interstitium. In addition, ADH up-regulates apical ENaC and urea transporters in the collecting duct, as well as $Na^+/K^+/2Cl^-$ cotransporters (NKCC2) in the thick ascending limb, to increase the concentration of solute in the interstitium and draw more water out of the collecting duct.

Inherited NDI, which is the major cause of NDI in children, typically results from mutations in either the V2 receptor or AQP-2 channel. V2 mutations account for 90% of cases and are inherited in an X-linked recessive pattern. Females may exhibit a variable level of disease depending on their particular pattern of X-inactivation (lyonization). AQP-2 mutations account for most of the remaining cases and can be inherited in an autosomal recessive or dominant pattern. Other tubular disorders, such as Bartter syndrome, can also feature increased urine production because of failure to establish an adequate concentration of solutes in the medullary interstitium; thus, even though ADH is present and functional, there is a diminished transcellular gradient for water transport.

Acquired NDI, which is more common in adults, is most frequently the result of long-term lithium usage, commonly employed to treat bipolar disorder. About 40% to 50% of patients who take lithium will experience this complication to some degree; among them, about half will experience significant polyuria, starting as early as 8 weeks after therapy begins. Lithium is freely filtered at the glomerulus and primarily reabsorbed in the proximal tubule. A small amount, however, is reabsorbed through apical ENaC in principle cells of the collecting duct. It accumulates within the cell, where it appears to interfere with the second messenger cascade that connects V2 activation to luminal insertion of AQP-2 channels. For reasons that are poorly understood, but which may involve a selective toxic effect on principal cells, these effects can persist even after lithium is discontinued.


DIABETES INSIPIDUS

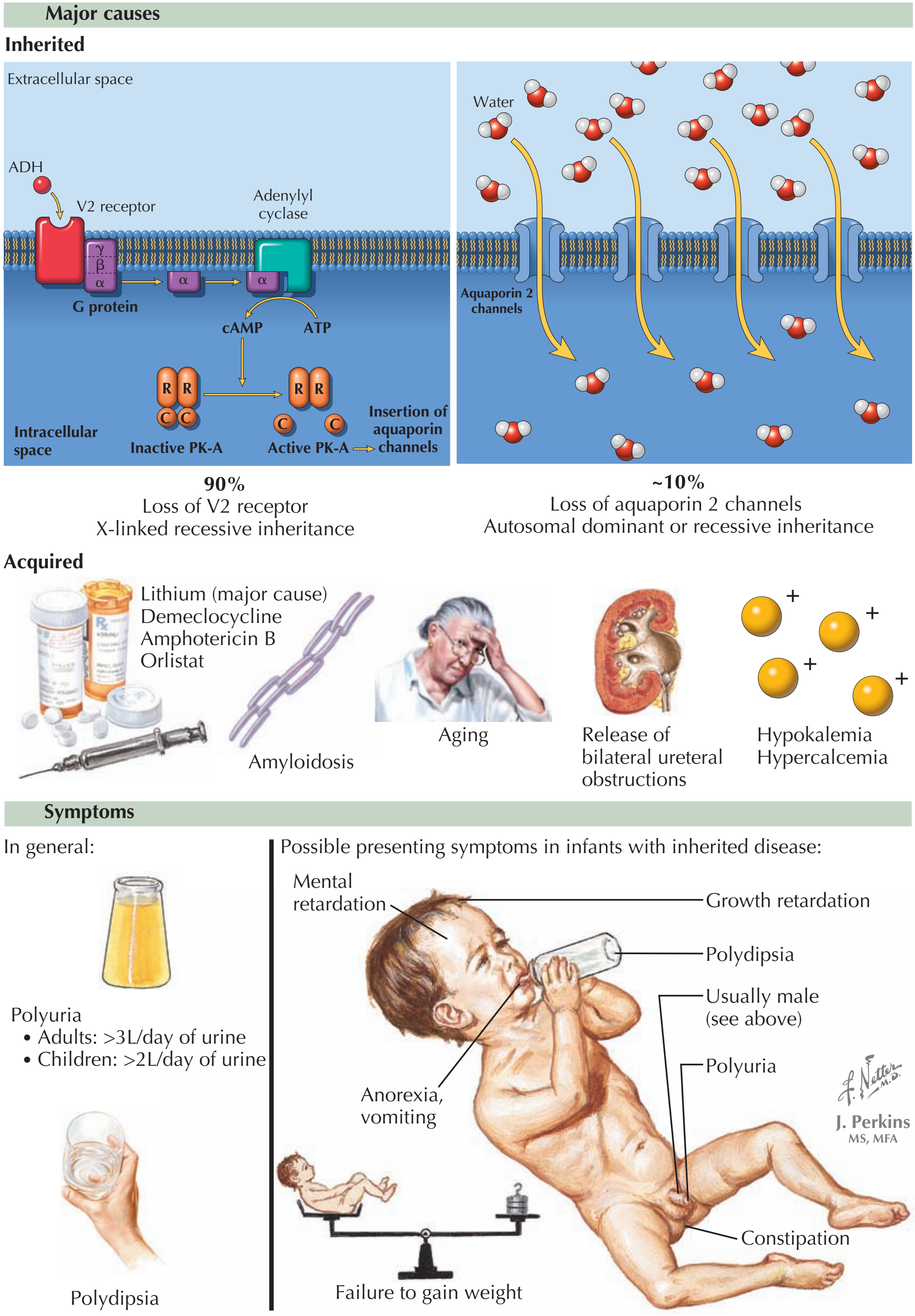
Central
Failure of osmoreceptors
Idiopathic destruction of hormone-producing cells
Neurosurgery
Trauma (skull fracture, hemorrhage, concussion)
Infection (meningitis, encephalitis, tuberculosis)
Tumors (craniopharyngioma, lymphoma, meningioma, pituitary tumor, metastasis)
Infiltration (Langerhans cell histiocytosis, sarcoidosis)
Inherited defects in ADH production
In supraoptic nucleus
In supraoptico-hypophysial tract
In neurohypophysis
Failure to produce ADH
F. Netter M.D.
Nephrogenic
Post.
Ant.
Pituitary gland
Normal central production of ADH
Filtration normal
Blood
ADH
Block
ADH
Block
Normal electrolyte reabsorption
Failure of water reabsorption
Renal tubules do not respond to endogenous or exogenous ADH
Large volumes of dilute urine

Other drugs that may cause diabetes insipidus include demeclocycline, amphotericin B, and orlistat. The mechanisms are diverse and not completely understood. V2 receptor antagonists, such as tolvaptan, may cause transient NDI. Finally, acquired NDI may also occur in the setting of normal aging, which causes a decreased density of collecting duct transporters; hypercalcemia and hypokalemia because these states interfere with reabsorption in the thick ascending limb and therefore decrease the medullary solute gradient; release of bilateral ureteral obstructions because of tubular injury; and amyloidosis, if there is extensive tubular deposition.

PRESENTATION AND DIAGNOSIS

The major symptom of both central and nephrogenic DI is polyuria, arbitrarily defined as greater than 3 L/day of urine production in adults and 2 L/day in children. Additional features often include constant thirst

MAJOR CAUSES AND SYMPTOMS OF NEPHROGENIC DIABETES INSIPIDUS


Major causes
Inherited
Extracellular space
ADH
V2 receptor
Adenylyl cyclase
γ
β
α
α
α
G protein
cAMP
ATP
R R
C C
Inactive PK-A
R R
C C
Active PK-A
Insertion of aquaporin channels
Intracellular space
Water
Aquaporin 2 channels
90%
Loss of V2 receptor
X-linked recessive inheritance
~10%
Loss of aquaporin 2 channels
Autosomal dominant or recessive inheritance
Acquired
Lithium (major cause)
Demeclocycline
Amphotericin B
Orlistat
Amyloidosis
Aging
Release of bilateral ureteral obstructions
Hypokalemia
Hypercalcemia
+
Symptoms
In general:
Polyuria
• Adults: >3L/day of urine
• Children: >2L/day of urine
Polydipsia
Possible presenting symptoms in infants with inherited disease:
Mental retardation
Growth retardation
Polydipsia
Usually male (see above)
Polyuria
Anorexia, vomiting
Constipation
Failure to gain weight
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J. Perkins MS, MFA

NEPHROGENIC DIABETES INSIPIDUS *(Continued)*

(polydipsia) and fatigue. In children with inherited NDI, failure to thrive and mental retardation may occur secondary to repeated episodes of severe dehydration, if diagnosis and treatment have been delayed.

Patients with polyuria should be questioned regarding their water intake to assess for possible primary polydipsia (i.e., compulsive water consumption, which leads by necessity to polyuria). In addition, their medications should be carefully reviewed to determine if they are taking diuretics or medications (such as lithium) known to cause DI. A prior history of trans-sphenoidal neurologic surgery strongly suggests central DI. Finally, family history should be assessed for possible inherited disease.

On serum chemistries, hypernatremia is suggestive of severe dehydration secondary to polyuria, whereas hyponatremia indicates primary polydipsia. Hypokalemia and hypercalcemia may cause NDI, as previously stated, and should be noted if present. Fasting glucose levels should be normal to exclude hyperglycemia as a cause of osmotic diuresis. Serum creatinine concentration may be slightly elevated in the setting of severe dehydration, with an elevated BUN:creatinine ratio and bland urine sediment suggestive of a prerenal state (see Plate 4-1).

In children and adults, a water deprivation test is the gold standard for diagnosis. This procedure tests the urine-concentrating capabilities of the kidneys in response to dehydration. In normal individuals, there will be an appropriate increase in urine osmolality as the body attempts to conserve free water. In patients with DI, in contrast, the urine osmolality remains depressed, with the exact level depending on various testing parameters and whether the DI is complete or partial. The distinction between central and nephrogenic DI may be established by assessing the response to exogenous vasopressin agonists, such as desmopressin, which will lead to urine concentration in central DI but have no effect in nephrogenic DI.

Of note, patients with primary polydipsia may have findings that resemble those of partial NDI because their urine-concentrating abilities are frequently impaired (as a result of medullary wash-out) but the addition of desmopressin has no effect (since they have intact secretion of endogenous ADH). Thus a careful history may be required to make the distinction.

TREATMENT

All potentially modifiable causes of NDI should be reversed. Lithium, for example, should be discontinued, and hypokalemia or hypercalcemia should be corrected. These measures may lead to complete recovery of renal function, although lithium-associated NDI may be irreversible in some cases.

It is important for all patients to maintain adequate hydration. If young children cannot obtain their own water, it must regularly be offered to them. A low-salt diet should be instituted to promote solute and water reabsorption in the proximal tubule.

In addition, a diuretic can be offered because it can paradoxically reduce urine output by causing a slight volume depletion, which up-regulates salt and water reabsorption in the proximal tubule. Thiazide diuretics are preferred over loop diuretics because the latter impair creation of the solute gradient in the medulla, which interferes with urine concentration. In addition, amiloride has been proposed as a potentially preventative measure in patients taking lithium, because this agent appears to limit lithium influx into principal cells. Its efficacy, however, remains unknown.

SECTION 4

RENAL DISEASES

OVERVIEW OF ACUTE KIDNEY INJURY

Acute kidney injury (AKI) consists of any precipitous decline in renal filtration function, which can occur secondary to disease affecting the renal vasculature, renal parenchyma, or urine collecting system. Such a decline is often first evidenced as an increase in serum creatinine concentration, which may be accompanied by normal urine output, oliguria, or anuria.

DEFINITION

Over time, various criteria have been proposed to define what degree of functional impairment constitutes AKI. The Acute Dialysis Quality Initiative (ADQI) created a consensus definition known as the RIFLE criteria, which stratifies patients based on serum creatinine concentration, estimated glomerular filtration rate (GFR), and urine output. A modification of these criteria was subsequently proposed by the Acute Kidney Injury Network (AKIN) since smaller changes in serum creatinine than proposed by the RIFLE criteria can have adverse effects on outcome. The criteria include:

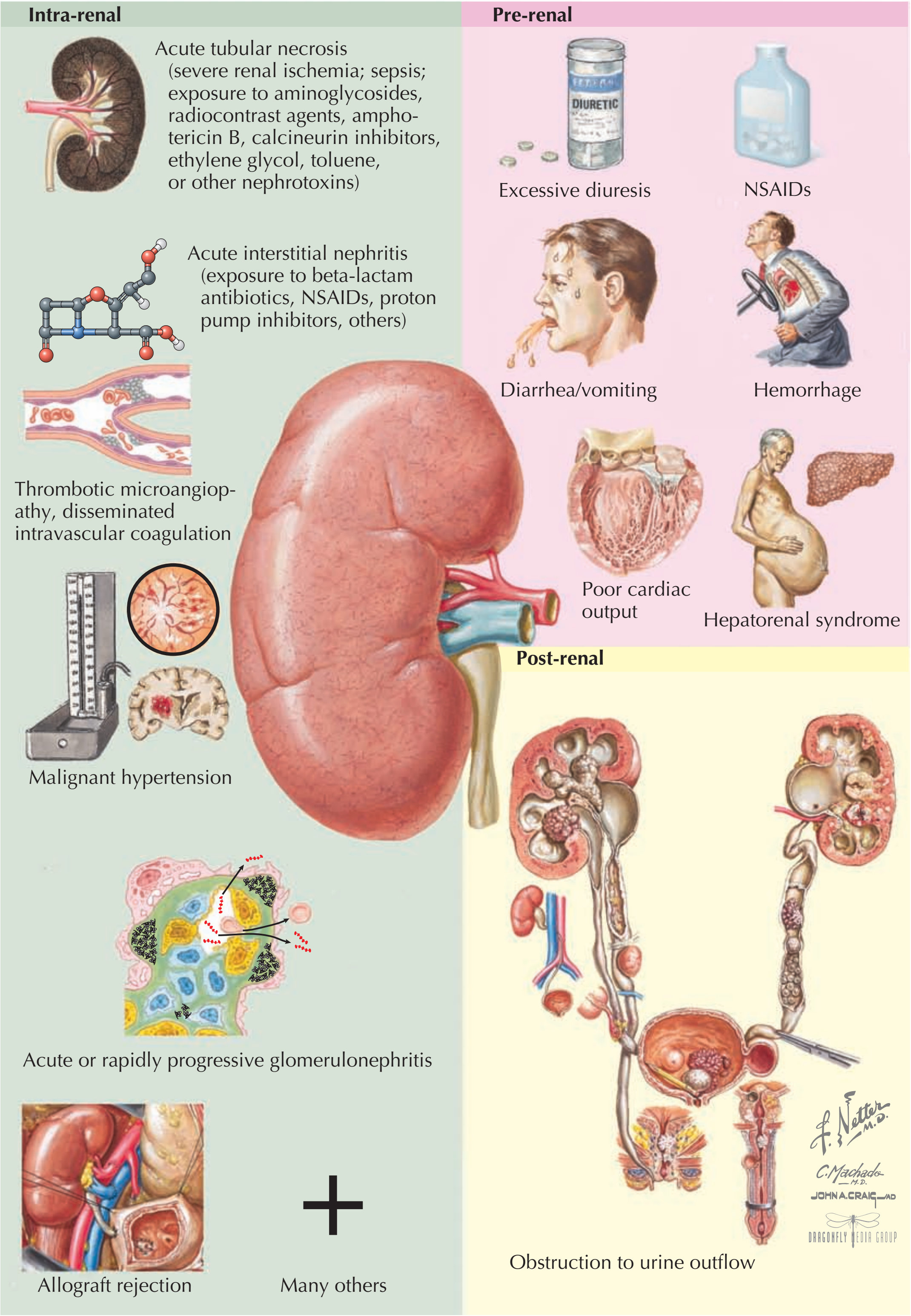
Stage 1 AKI: increase in serum creatinine by ≥0.3 mg/dL or by 150% to 200%, OR urine output <0.5 mL/kg/hr for 6 hours

Stage 2 AKI: increase in serum creatinine by 200% to 300%, OR urine output <0.5 mL/kg/hr for 12 hours

Stage 3 AKI: increase in serum creatinine by >300% or to more than 4.0 mg/dL with an acute increase of greater than 0.5 mL/dL, OR urine output <0.3 mL/kg/hr for 24 hours, anuria for 12 hours or renal replacement therapy

These diagnoses should be applied only if the decline in renal function occurs over a rapid time course (i.e., less than 48 hours). There are several issues that may complicate application of these criteria. First, they require knowledge of the patient's baseline renal function. Second, serum creatinine concentrations may not be in a steady state in patients with declining renal function. Research efforts into more sensitive biomarkers of renal injury, such as cystatin C and neutrophil gelatinase-associated lipocalin (NGAL), are ongoing but have not yet had a wide impact on clinical practice.

CAUSES OF ACUTE KIDNEY INJURY


Intra-renal
Acute tubular necrosis (severe renal ischemia; sepsis; exposure to aminoglycosides, radiocontrast agents, amphotericin B, calcineurin inhibitors, ethylene glycol, toluene, or other nephrotoxins)
Acute interstitial nephritis (exposure to beta-lactam antibiotics, NSAIDs, proton pump inhibitors, others)
Thrombotic microangiopathy, disseminated intravascular coagulation
Malignant hypertension
Acute or rapidly progressive glomerulonephritis
Allograft rejection
+
Many others
Pre-renal
DIURETIC
Excessive diuresis
NSAIDs
Diarrhea/vomiting
Hemorrhage
Poor cardiac output
Hepatorenal syndrome
Post-renal
Obstruction to urine outflow
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DRAGONFLY MEDIA GROUP

CLASSIFICATION OF ETIOLOGIES

The various etiologies responsible for AKI are typically categorized as "prerenal," "intrarenal," or "postrenal."

Prerenal. "Prerenal" AKI, the most common kind (60% of cases), reflects a significant reduction in renal perfusion. Mild reductions in renal perfusion do not affect the glomerular filtration rate (GFR) because of compensatory feedback responses, such as activation of the renin-angiotensin system and release of vasodilatory prostaglandins (see Plate 3-18). In the setting of markedly reduced flow, however, these compensatory mechanisms fail, and renal filtration declines. By definition, however, the renal parenchyma remains intact, and normal function can be restored with intravascular fluid repletion.

Common causes of prerenal AKI include excessive diuresis, diarrhea, vomiting, hemorrhage, burns, poor cardiac output (i.e., congestive heart failure, see Plate 4-38), liver failure (i.e., hepatorenal syndrome, see Plate 4-40), and hypercalcemia (due to renal vasoconstriction). In addition, patients with low baseline renal perfusion may experience prerenal AKI if their normal compensatory mechanisms are blocked by either nonsteroidal antiinflammatory drugs (e.g., ibuprofen), which interfere with tubuloglomerular feedback, or inhibitors of the renin-angiotensin system (i.e., angiotensin-converting enzyme [ACE] inhibitors, aldosterone receptor blockers [ARBs]).

Patients with prerenal AKI may exhibit other signs of volume depletion, such as tachycardia, orthostatic hypotension, and dry mucous membranes. In addition, prerenal AKI can be distinguished from other causes by the intense reabsorption of solutes that results from the normal renal response to decreased perfusion. Specifically the fractional excretion of sodium (FENa, see Plate 3-6 for formula) should be low (<1%); the serum blood urea nitrogen (BUN):creatinine ratio may be elevated (i.e., >20 : 1), reflecting increased reabsorption

OVERVIEW OF ACUTE KIDNEY INJURY *(Continued)*

of urea; and the urine should be concentrated (>500 mOsm/kg H_2O). Note that FENa values may be invalid among patients who have recently taken diuretics; in this case, the fractional excretion of urea has been proposed as an alternative means of assessing tubular reabsorption because it is generally less than 35% in the prerenal state. Finally, because the renal parenchyma is not damaged, the urine sediment should not contain red blood cells, white blood cells, or other markers of renal inflammation. Hyaline casts, however, may be seen; these occur because low tubular flow rates increase aggregation of Tamm-Horsfall mucoproteins, which are secreted by the distal tubular epithelium.

Once prerenal AKI is suspected, the diagnosis can be confirmed by documenting normalization of renal function upon resuscitation of intravascular volume.

Intrarenal. "Intrarenal" AKI, the second most common kind (35% of cases), reflects direct damage to the renal parenchyma. Acute tubular necrosis (ATN, see Plate 4-3) accounts for nearly 90% of cases and is by far the most common cause. ATN occurs in the setting of either severe renal ischemia or direct toxic damage to the renal tubules by either extrinsic toxins (such as aminoglycosides or radiocontrast agents) or intrinsic toxins (such as myoglobin or hemoglobin). The many other causes of intrarenal AKI include acute or rapidly progressive glomerulonephritis (GN, see Plate 4-14), thrombotic microangiopathy (see Plate 4-32), disseminated intravascular coagulation, malignant hypertension (see Plate 4-44), acute interstitial nephritis (AIN, see Plate 4-28), and post-transplant renal allograft rejection.

Unlike prerenal AKI, intrarenal AKI does not improve in response to an intravenous fluid bolus. In addition, it generally does not produce evidence of increased tubular reabsorption. Thus the FENa is often >2%, the BUN : creatinine ratio is 10 to 15 : 1, and the urine osmolality is ≤400 mOsm/kg.

Intrarenal AKI may also be distinguished by findings on urine microscopy that indicate glomerular or tubular damage. ATN, for example, is often (but not always) associated with "muddy brown" pigmented granular casts or tubular epithelial cell casts. GN is associated with evidence of glomerular bleeding (dysmorphic red blood cells [RBCs], red blood cell casts; see Plate 4-14 for details). AIN is associated with white blood cell casts, white blood cells, and RBCs. In addition, glomerular and interstitial diseases are often associated with proteinuria, unlike prerenal or postrenal disease.

Finally, several glomerulonephritides cause abnormal complement levels, which are generally not seen in prerenal or postrenal disease unless the patient has other comorbidities. Additional details are available later in this section.

Once intrarenal AKI is suspected, the diagnosis of ATN is often reached based on history and laboratory findings. If a cause other than ATN appears likely, however, and the patient's renal function is not improving, a renal biopsy is often performed.

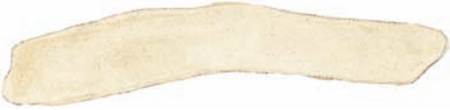
Postrenal. "Postrenal" AKI, the least common kind (5% of cases), reflects obstruction to urine flow from both kidneys (or in a solitary kidney). The obstructions must therefore affect the urethra, bladder neck, or both ureters. Such obstructions are often associated with intense flank and groin pain, which results from stretching of the proximal collecting system. Although flank pain may also occur in intrinsic renal diseases, referred pain to the groin indicates lower tract inflammation and is more suggestive of obstruction. The patient may offer a history of weak urine stream or incomplete emptying. On examination, an enlarged bladder or prostate (in men) may be palpable. Microscopic analysis of urine may be unremarkable or may reveal RBCs in the case of nephrolithiasis.

Once postrenal AKI is suspected, the patient should undergo further evaluation with radiographic imaging to further characterize the obstruction.

MANAGEMENT

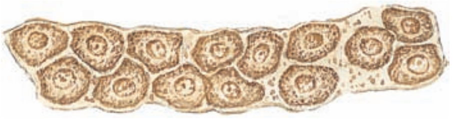
The specific management of these various etiologies is discussed later in this book. Irrespective of the cause, however, clinicians should be cognizant of the common sequelae of severely impaired renal function, such as fluid retention (with subsequent hypertension and edema), hyperkalemia, and metabolic acidosis. Any of these conditions, if not correctable with medications, may require renal replacement therapy.

POSSIBLE URINE SEDIMENT FINDINGS IN ACUTE KIDNEY INJURY



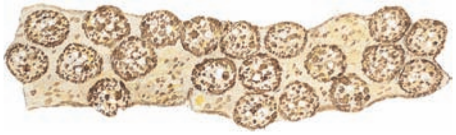
Hyaline casts

- Seen in normal individuals and pre-renal state
- Formed by aggregation of Tamm-Horsfall mucoprotein in distal tubule, especially when there is low urine flow



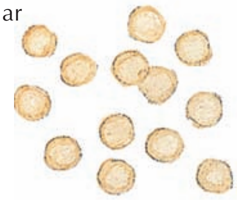
Epithelial cell casts

- Formed by sloughed renal tubular cells and Tamm-Horsfall mucoprotein in distal tubule
- Often (but not always) seen in acute tubular necrosis



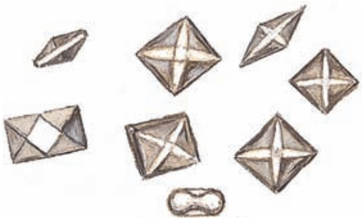
White blood cell casts

- Formed by leukocytes that enter tubules and aggregate with Tamm-Horsfall mucoprotein
- Seen in acute interstitial nephritis, exudative glomerulonephritis, and severe pyelonephritis



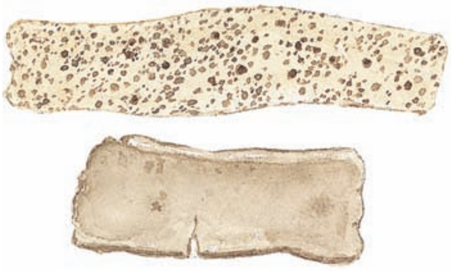
Red blood cells

- May reflect glomerular disease, papillary necrosis, pyelonephritis, cystitis, urinary tract malignancy, urolithiasis, and many others



Oxalate crystals

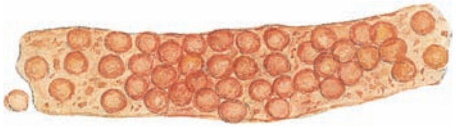
- May be seen with calcium oxalate stones
- Also indicate ethylene glycol ingestion or other hyperoxaluria



Coarsely granular casts

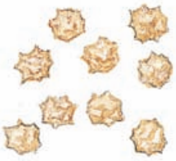
Waxy casts

- Formed by the breakdown of cellular casts
- Non-specific indicators of intrarenal disease
- "Muddy brown" pigmentation of coarsely granular casts may be seen in acute tubular necrosis



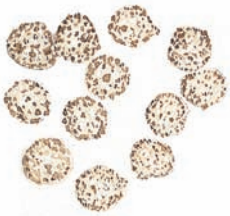
Red blood cell casts

- Formed by red blood cells that enter the tubules at the glomerulus and then aggregate with Tamm-Horsfall mucoprotein
- Indicate glomerular disease



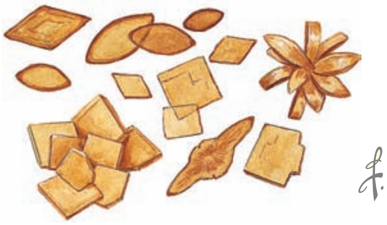
Dysmorphic red blood cells

- Formed as red blood cells pass through pores in damaged glomerular capillaries
- Indicate glomerular disease



White blood cells

- Major causes are cystitis, pyelonephritis, and acute interstitial nephritis



F. Netter M.D.

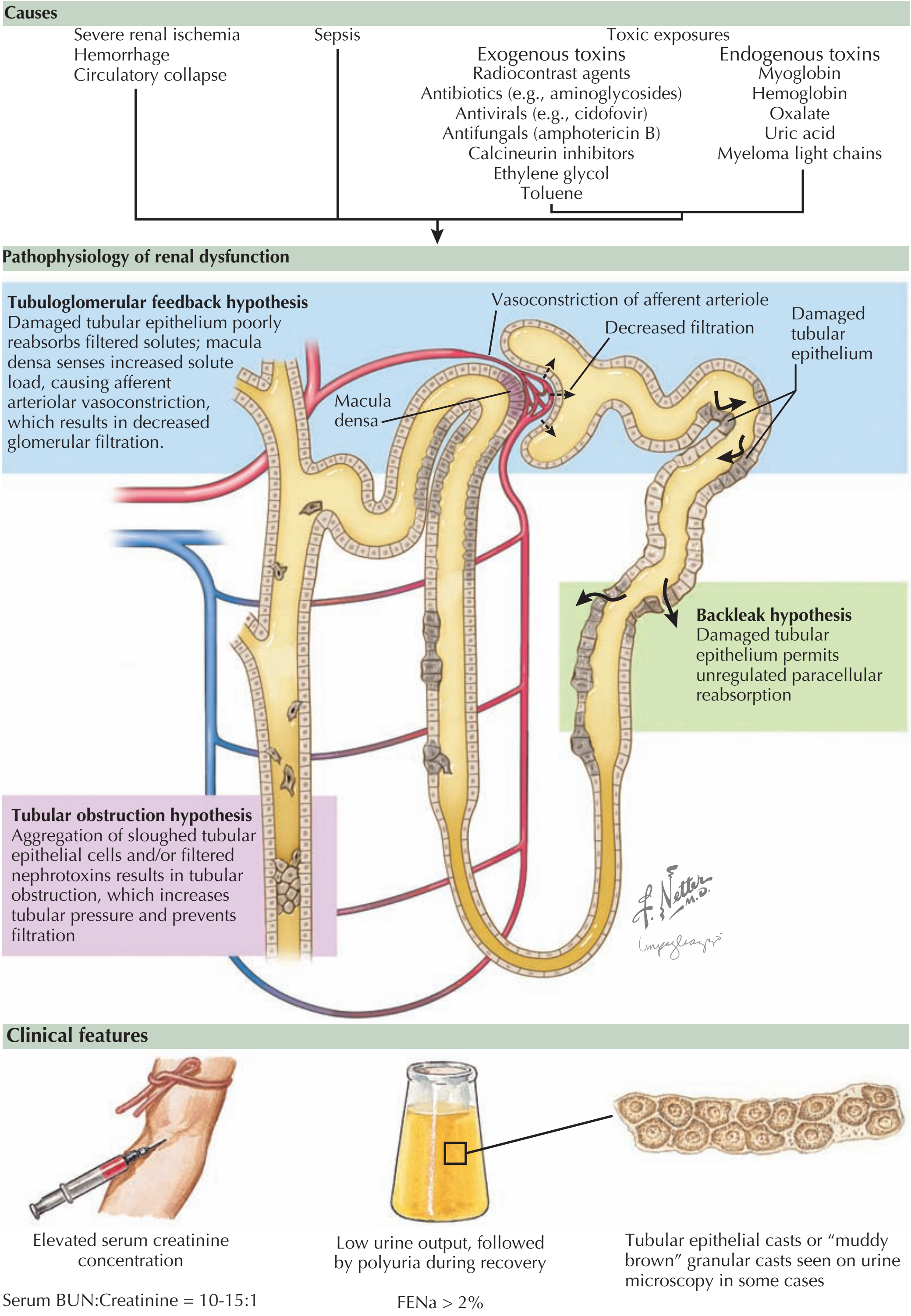
Uric acid crystals

- May be seen with uric acid stones
- May also be seen in tumor lysis syndrome

ACUTE TUBULAR NECROSIS

Acute tubular necrosis (ATN) is one of the most common causes of acute kidney injury (AKI), accounting for over 90% of intrarenal AKI. It is characterized by a sudden decline in glomerular filtration rate (GFR) as a result of direct tubular damage.

CAUSES, PATHOPHYSIOLOGY, AND CLINICAL FEATURES OF ACUTE TUBULAR NECROSIS


Causes
Severe renal ischemia
Hemorrhage
Circulatory collapse
Sepsis
Toxic exposures
Exogenous toxins
Radiocontrast agents
Antibiotics (e.g., aminoglycosides)
Antivirals (e.g., cidofovir)
Antifungals (amphotericin B)
Calcineurin inhibitors
Ethylene glycol
Toluene
Endogenous toxins
Myoglobin
Hemoglobin
Oxalate
Uric acid
Myeloma light chains
Pathophysiology of renal dysfunction
Tubuloglomerular feedback hypothesis
Damaged tubular epithelium poorly reabsorbs filtered solutes; macula densa senses increased solute load, causing afferent arteriolar vasoconstriction, which results in decreased glomerular filtration.
Vasoconstriction of afferent arteriole
Decreased filtration
Damaged tubular epithelium
Macula densa
Backleak hypothesis
Damaged tubular epithelium permits unregulated paracellular reabsorption
Tubular obstruction hypothesis
Aggregation of sloughed tubular epithelial cells and/or filtered nephrotoxins results in tubular obstruction, which increases tubular pressure and prevents filtration
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Clinical features
Elevated serum creatinine concentration
Serum BUN:Creatinine = 10-15:1
Low urine output, followed by polyuria during recovery
FENa > 2%
Tubular epithelial casts or "muddy brown" granular casts seen on urine microscopy in some cases

PATHOPHYSIOLOGY

ATN is typically classified as ischemic, septic, or toxic.

Ischemic ATN occurs when there is a decrease in renal perfusion that is severe and sustained enough to injure the tubular epithelium. Such damage typically occurs in the setting of circulatory collapse or massive hemorrhage.

Septic ATN involves direct cytokine-induced damage to the renal tubules. Ischemic damage may also occur if there is extensive systemic vasodilation.

Toxic ATN has been associated with numerous toxins that damage the tubular epithelium through a variety of mechanisms, which include production of free radicals, constriction of renal microvasculature, and tubular obstruction (i.e., via formation of crystals and/or casts). Major exogenous toxins include iodinated radiocontrast agents, antibiotics (e.g., aminoglycosides), antivirals (e.g., cidofovir), antifungals (e.g., amphotericin B), calcineurin inhibitors (e.g., cyclosporine and tacrolimus), ethylene glycol, and toluene. Major endogenous toxins include myoglobin, hemoglobin, oxalate, uric acid (i.e., in tumor lysis syndrome), and myeloma light chains. In fact, the first cases of ATN, described in World War II, were likely the result of excessive myoglobin released into the circulation during crush injuries.

Although these agents injure the tubular epithelium, the structural damage is often inadequate to explain the dramatic decline in the overall glomerular filtration rate. In addition, creatinine undergoes a far greater degree of filtration than secretion, but serum concentrations are nonetheless markedly elevated. Thus three mechanisms have been proposed to relate the physiologic findings to the histologic changes: (1) tubuloglomerular feedback, (2) tubular obstruction, and (3) back leak.

The "tubuloglomerular feedback" hypothesis argues that tubular damage results in decreased proximal reabsorption of electrolytes, including sodium and chloride, which leads to elevated concentrations of these solutes at the macula densa. Through the mechanisms described in Plate 3-18, the macula densa triggers intense vasoconstriction of the afferent arteriole, which reduces the filtration rate.

The "tubular obstruction" hypothesis argues that sloughing of epithelial cells into the tubular lumen produces obstructive casts, which increase the hydrostatic pressure in Bowman's space and thereby decrease filtration.

The "back leak" hypothesis argues that the damaged tubular epithelium and endothelium permits paracellular reabsorption of filtered molecules, including creatinine, into the interstitium.

The prevailing opinion among nephrologists is that the tubuloglomerular feedback hypothesis accounts for a majority of the observed decline in filtration, although it is possible that all three mechanisms contribute to some degree.

PRESENTATION AND DIAGNOSIS

The clinical course is generally divided into three phases: initiation, maintenance, and recovery. The initiation phase corresponds to the period during which the patient is exposed to the toxic insult and experiences an immediate decline in GFR and urine output. The maintenance phase occurs after the renal injury is established but before recovery occurs, and it is characterized by a stable but low GFR. This phase has been reported to last between several hours and several months, with a median length of 1 to 3 weeks. The recovery phase, if it occurs at all, corresponds to regeneration of renal tubules and normalization of renal function. This period is often associated with polyuria because of the impaired concentrating ability of immature tubular cells. Eventually, reabsorption capacity returns to normal, and polyuria ceases.

The first manifestation of disease is typically a sharp increase in serum creatinine concentration on routine laboratory examination. Recent exposure to a known nephrotoxin strongly suggests the diagnosis of ATN, whereas hemodynamic compromise may cause either prerenal state or ATN. Thus distinguishing between prerenal state and ATN is often an important part of the differential diagnosis. As described in the overview of AKI, the distinction between prerenal and intrarenal disease can often be established based on the response to an intravenous fluid bolus, as well as laboratory markers such as FENa and the BUN:creatinine ratio. Microscopic analysis of urine may also facilitate the

ACUTE TUBULAR NECROSIS

(Continued)

diagnosis. In the prerenal state, urine either appears normal or contains hyaline casts, which form when Tamm-Horsfall protein, secreted in the distal tubule, becomes concentrated and aggregates. In contrast, ATN often features "muddy-brown" granular casts or epithelial casts.

These laboratory indicators, however, can sometimes be unreliable. Contrast-induced ATN, for example, initially causes a high BUN : creatinine ratio and low FENa, which could be misinterpreted as evidence of prerenal state. Instead, these values reflect the intense renal vasoconstriction associated with contrast agents. For as long as the tubular epithelium remains intact, such vasoconstriction causes increased sodium reabsorption. As the ischemia persists, however, tubular cells become injured and their ability to reabsorb sodium is lost, leading to laboratory values more consistent with ATN.

The diagnosis of ATN is typically established based on clinical and laboratory criteria. Renal biopsy is generally not performed unless intrarenal AKI secondary to another cause, such as rapidly progressive glomerulonephritis (see Plate 4-25), is suspected. Nonetheless, ATN is associated with a spectrum of common pathologic findings, irrespective of the cause, which can include shortening or loss of the proximal tubular brush border, epithelial cell flattening and simplification, nucleolar prominence, hypereosinophilia, and sloughing of tubular epithelial cells. Despite the name, actual frank necrosis is only an occasional finding. The degree of injury is often dependent on the severity of the exposure, rather than the identity of the specific agent. These pathologic changes can occur in both proximal and distal nephron segments.

TREATMENT

The treatment of ATN consists of identifying and eliminating the underlying cause, as well as implementing supportive measures and initiating renal replacement therapy when appropriate. Supportive strategies include strict attention to fluids and electrolytes, as well as limiting the administration of substances that undergo primarily renal clearance. If these strategies are followed, dialysis can often be avoided in cases of prolonged ATN. For example, furosemide can be used to increase diuresis, which can treat volume overload and hyperkalemia. Likewise, bicarbonate can be used to correct acidemia. Occasionally, severe cases of ATN cannot be managed supportively, and dialysis must be initiated. The major indications include acidosis, fluid overload, and hyperkalemia that are refractory to medical management, as well as signs of uremia such as pericarditis or encephalopathy. There are no proven therapies that "reverse" ATN.

PROGNOSIS

Because there are no effective therapies that reverse the clinical or pathologic changes associated with ATN, mortality remains high and, despite decades of intense research, has not changed over the past 50 years. Mortality rates have been reported to be up to 40% in hospitalized patients with ATN and up to 80% in critically ill patients with ATN.

Many patients who survive ATN experience an eventual normalization of renal function. Some, however, sustain moderate to severe tubulointerstitial scarring that leads to chronic kidney disease (CKD), with about 5% to 10% ultimately requiring long-term dialysis. Risk factors for nonresolving renal function after ATN include persistent septic physiology, recurrent nephrotoxin administration, and preexisting chronic kidney disease.

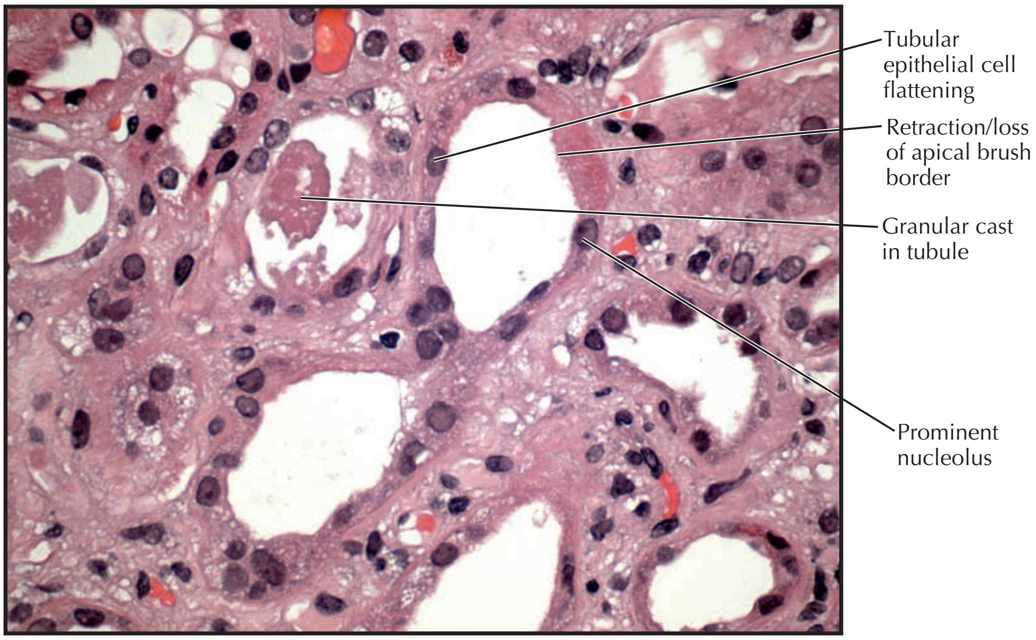
PREVENTION

The most effective prevention strategy is to maintain euvolemia in hospitalized patients and to avoid excessive exposure to nephrotoxic agents, especially in patients with preexisting renal disease.

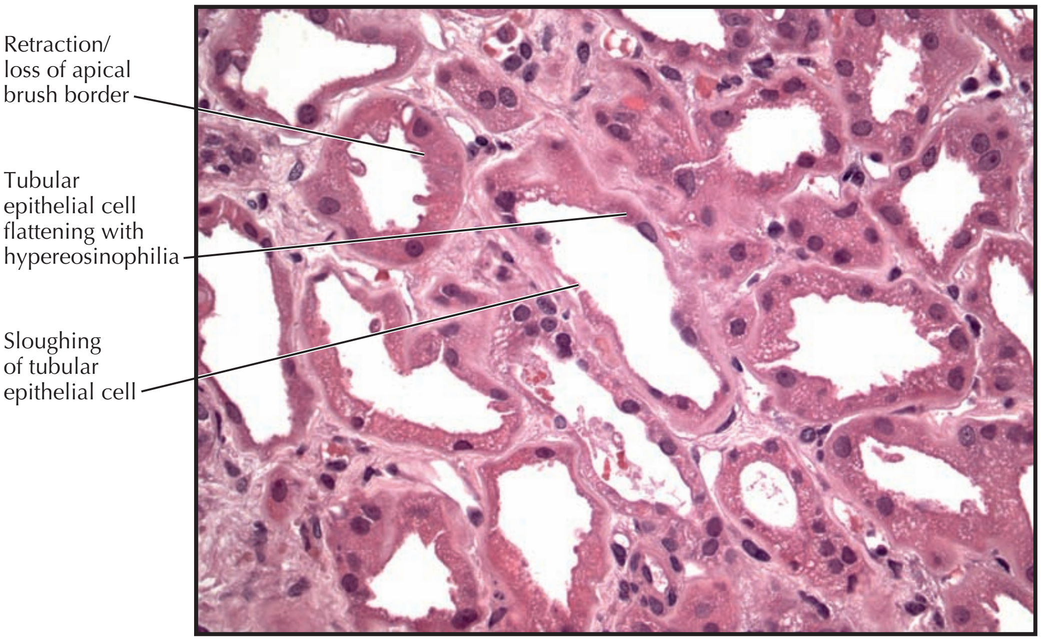
In situations where ATN could be expected, such as during administration of intravenous radiocontrast, maintaining euvolemia and limiting the dye load might be expected to reduce the risk of this complication. Other measures—including the use of antioxidants, natriuretic peptides, and high dose furosemide/mannitol—have not been shown to consistently decrease the risk of ATN.

Multiple risk scores have been devised to predict which patients are at highest risk for developing ATN and which will have the poorest outcome. The risk factors overlap, and they include variables that predict preexisting histologic damage and at predispose to renal ischemia, including male sex, advanced age, comorbid illness, malignancy, volume depletion/oliguria, sepsis, and multiorgan failure.

HISTOPATHOLOGIC FINDINGS OF ACUTE TUBULAR NECROSIS

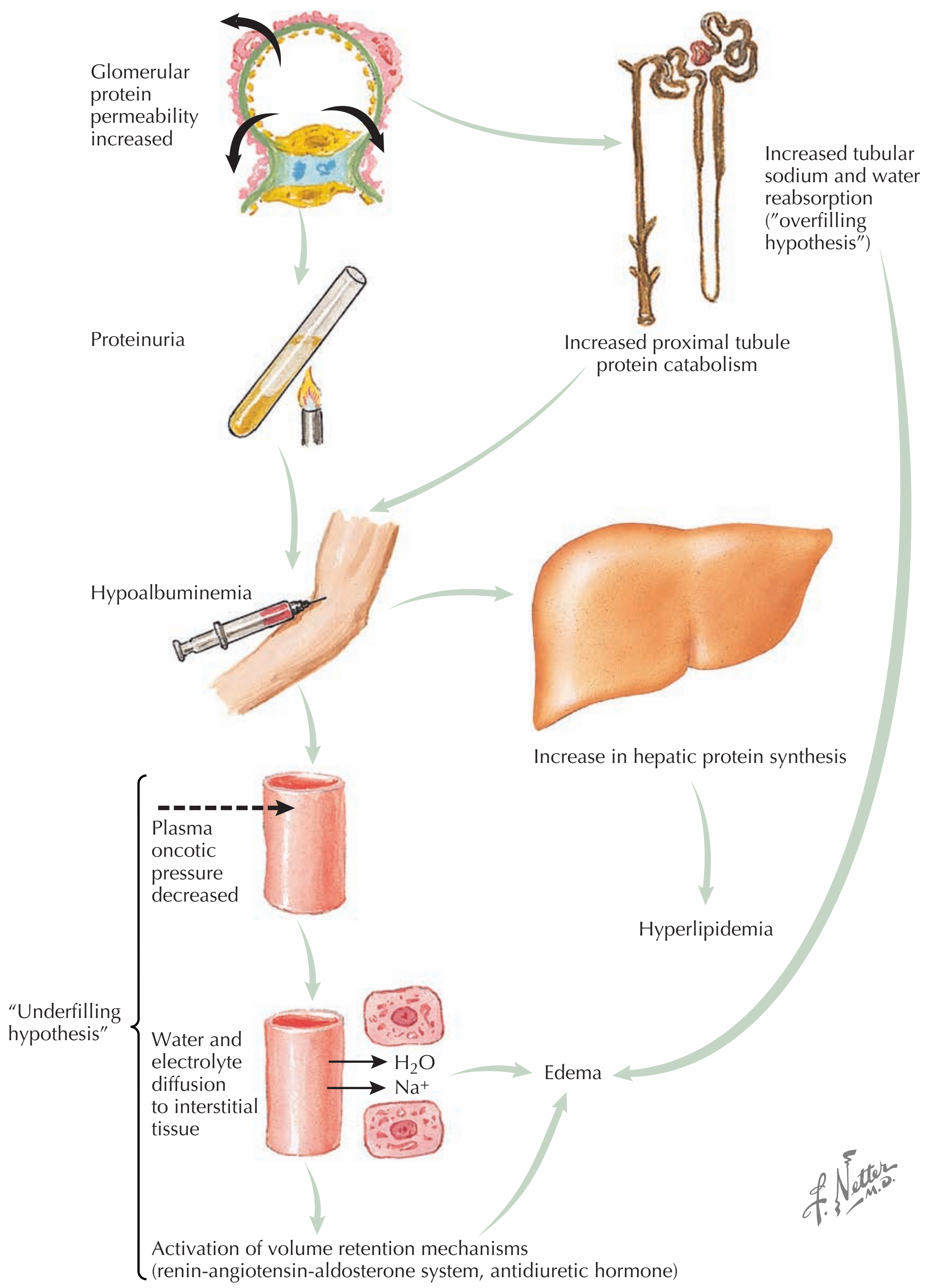

Tubular epithelial cell flattening
Retraction/loss of apical brush border
Granular cast in tubule
Prominent nucleolus

PAS stain


Retraction/ loss of apical brush border
Tubular epithelial cell flattening with hypereosinophilia
Sloughing of tubular epithelial cell

H and E stain

PATHOPHYSIOLOGY OF NEPHROTIC SYNDROME


Glomerular protein permeability increased
Proteinuria
Hypoalbuminemia
Plasma oncotic pressure decreased
"Underfilling hypothesis"
Water and electrolyte diffusion to interstitial tissue
H_2O
Na^+
Edema
Activation of volume retention mechanisms (renin-angiotensin-aldosterone system, antidiuretic hormone)
Increased tubular sodium and water reabsorption ("overfilling hypothesis")
Increased proximal tubule protein catabolism
Increase in hepatic protein synthesis
Hyperlipidemia

OVERVIEW OF NEPHROTIC SYNDROME

The nephrotic syndrome encompasses a constellation of clinical and laboratory findings related to the loss of large quantities of protein in urine. The major symptom is edema, and the laboratory findings include (1) "nephrotic-range" proteinuria, defined in adults as more than 3.5 g of protein excretion per 24 hours, (2) hypoalbuminemia, and (3) hyperlipidemia. The threshold for nephrotic proteinuria in children is lower and depends on body weight.

PATHOPHYSIOLOGY

"Nephrotic syndrome" is a nonspecific diagnosis that suggests underlying glomerular disease. The normal, noninflamed glomerulus forms a tight barrier to proteins, such as albumin, largely because of the slit diaphragms that connect podocyte (visceral epithelial cell) foot processes on the outside surface of the glomerular basement membrane.

In nephrotic syndrome, inflammation disrupts the normal structure of the slit diaphragms, permitting the passage of potentially large amounts of protein into the urine. In most cases, the foot processes appear "fused" or "effaced," meaning that a continuous layer of podocyte cytoplasm is seen over the glomerular capillaries, rather than the discrete, individual processes seen in the normal state. Such effacement reflects widening, shortening, and retraction of the foot processes. Although the glomerular inflammation is typically not severe enough to cause an acute decline in overall filtration, scarring and loss of renal function may occur over time.

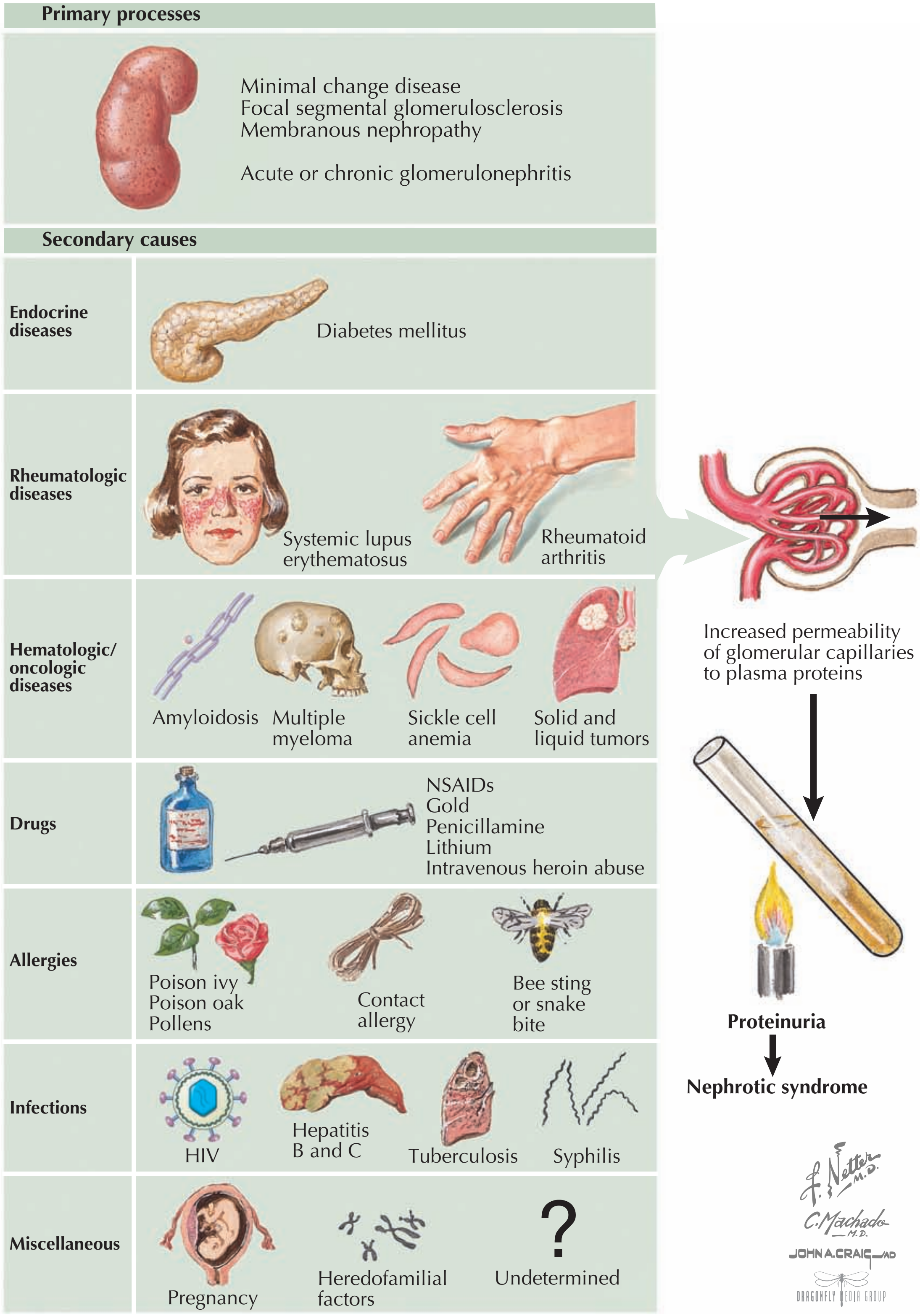
The ongoing loss of albumin into urine causes hypoalbuminemia. The decline in serum albumin concentration, however, is often out of proportion to the degree of proteinuria. One possible explanation is that the proximal tubular catabolism of albumin is accelerated because of the increased filtered load.

In response to the low serum albumin concentrations, the liver increases its production of numerous proteins, including lipoproteins, leading to hyperlipidemia.

Edema occurs for at least two possible reasons. The first, known as the "underfilling hypothesis," argues that low serum albumin concentrations lead to a reduction in intravascular oncotic pressure. As a result, plasma moves from the capillary lumen to the interstitium, which leads to edema. The resulting intravascular depletion activates the renin-angiotensin-aldosterone system, which promotes retention of sodium and water and thus further worsens the edema. The second hypothesis, known as the "overfilling hypothesis," argues that there is primary retention of sodium at the level of the collecting duct, perhaps triggered by the filtered proteins themselves, that leads to edema. It appears probable that both hypotheses are correct, and that the primary mechanism for edema may vary across patients and across time.

Patients with nephrotic syndrome are at increased risk for lower extremity, pulmonary, and renal vein thromboses (see Plate 4-35) because of urinary losses of anticoagulant proteins, such as antithrombin and plasminogen, as well as increased hepatic production of procoagulant proteins, such as fibrinogen and other clotting factors. Among the nephrotic syndromes, thromboses are most often seen in patients with membranous nephropathy, but any patient with proteinuria above 10 g/day and albumin levels below 2 g/dL should be considered at risk.

Causes of Nephrotic Syndrome


Primary processes
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute or chronic glomerulonephritis
Secondary causes
Endocrine diseases
Diabetes mellitus
Rheumatologic diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Hematologic/ oncologic diseases
Amyloidosis
Multiple myeloma
Sickle cell anemia
Solid and liquid tumors
Drugs
NSAIDs
Gold
Penicillamine
Lithium
Intravenous heroin abuse
Allergies
Poison ivy
Poison oak
Pollens
Contact allergy
Bee sting or snake bite
Infections
HIV
Hepatitis B and C
Tuberculosis
Syphilis
Miscellaneous
Pregnancy
Heredofamilial factors
?
Undetermined
Increased permeability of glomerular capillaries to plasma proteins
Proteinuria
Nephrotic syndrome

OVERVIEW OF NEPHROTIC SYNDROME *(Continued)*

CAUSES AND EPIDEMIOLOGY

Three primary glomerular diseases—minimal change disease (MCD, see Plate 4-8), focal segmental glomerulosclerosis (FSGS, see Plate 4-10), and membranous nephropathy (MN, see Plate 4-12)—all cause significant proteinuria, which is often sufficient to result in nephrotic syndrome.

Other primary glomerular diseases, such as the various glomerulonephritides (see Plate 4-14), typically cause proteinuria, hematuria, and a variable degree of renal dysfunction. In a subset of cases, the proteinuria is sufficient to result in nephrotic syndrome.

Finally, many systemic conditions or environmental agents can cause nephrotic syndrome, either by causing a distinct pattern of glomerular inflammation (i.e., amyloidosis see Plate 4-47], diabetes mellitus [see Plate 4-45]) or by causing one of the renal diseases listed previously. Examples of the latter include secondary MCD in the setting of lymphoma, infection (e.g., tuberculosis), allergies, and lithium or NSAID use; secondary FSGS in the setting of HIV infection, heroin abuse, and sickle cell disease; and secondary MN in the setting of systemic lupus erythematosus, rheumatoid arthritis, viral hepatitis infection, syphilis, penicillamine use, gold poisoning, and solid tumors in general.

In both children and adults, the annual incidence of nephrotic syndrome is approximately five cases per 100,000 individuals. This incidence, however, likely underestimates the true disease burden because many cases, especially those secondary to diabetes, do not undergo biopsy-proven diagnosis.

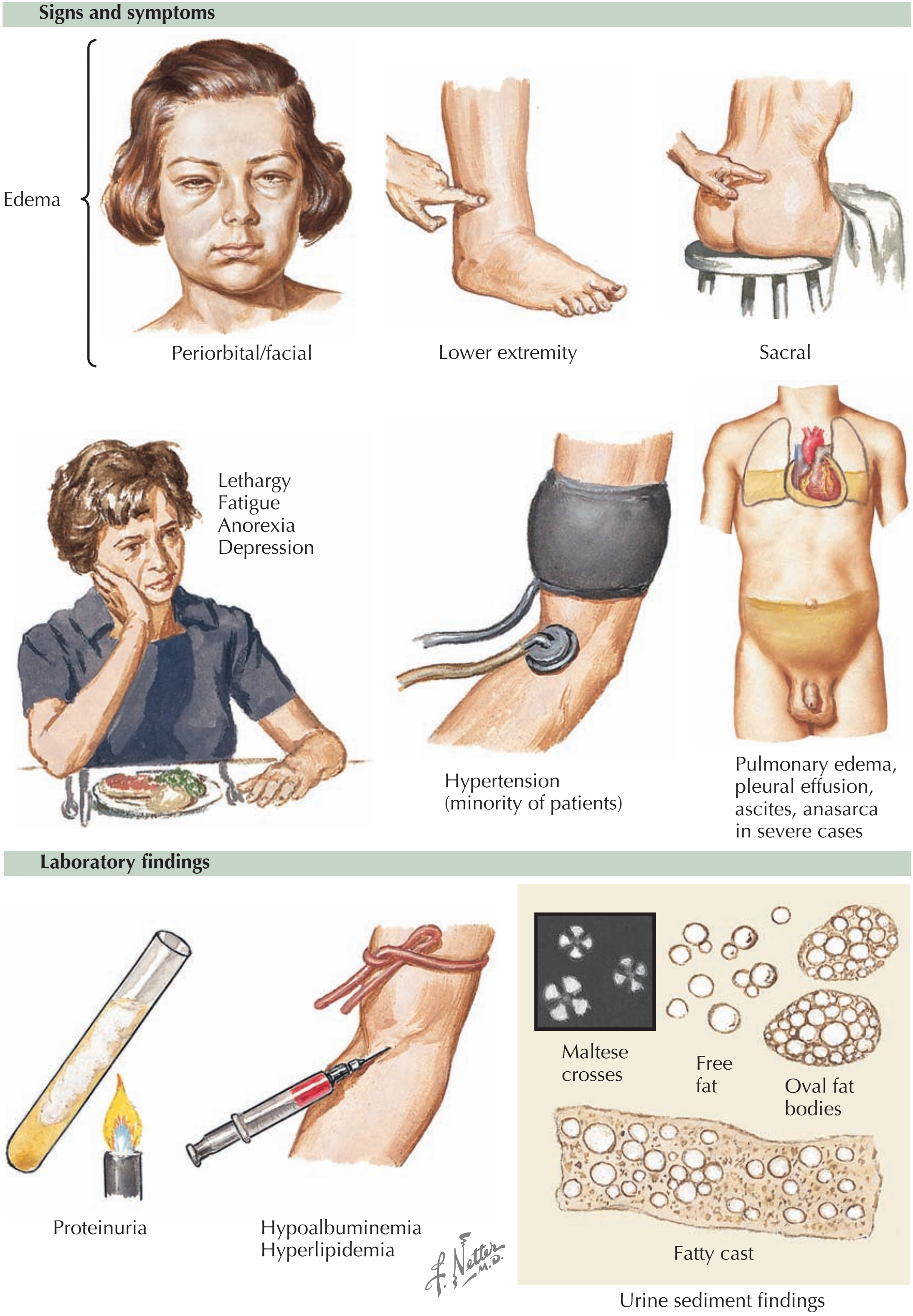
There are strong age and race predilections for the various causes of nephrotic syndrome. In children, the most common cause by far is MCD. In adults, the most common cause of secondary nephrotic syndrome is diabetes mellitus, whereas the two most common causes of idiopathic nephrotic syndrome are MN and FSGS. Until recently, MN was the most common cause in white adults, whereas FSGS was the most common cause in black adults. More recent data, however, shows a steadily rising incidence of FSGS, in part because of the large number of cases occurring secondary to obesity. As a result, FSGS may soon emerge as the most common cause of idiopathic nephrotic syndrome in all adults.

PRESENTATION AND DIAGNOSIS

Edema is the most common presenting symptom. Gravity increases intracapillary hydrostatic pressure and is thus the major determinant of the extravascular fluid distribution. Thus edema is typically most severe in the lower extremities; however, after sleeping in a prone position, the patient may experience swelling of the face, especially in the periorbital region. Severe fluid retention can also lead to pulmonary edema (with associated shortness of breath), effusions, or frank anasarca. Hypertension may occur in a minority of patients. Finally, patients may also describe weakness, malaise, and a "foamy" or "bubbly" appearance to their urine.

Patients with edema do not necessarily have nephrotic syndrome, since other diseases—notably congestive heart failure and cirrhosis—can present in this fashion. The diagnosis of nephrotic syndrome is suggested, however, when urine dipstick reveals marked proteinuria. Urine microscopy may reveal oval fat bodies, lipid droplets, and fatty casts (which resemble "Maltese crosses" under polarized light), which reflect the presence of lipoproteins in the urine. The presence of dysmorphic red blood cells and red cell casts suggests the proteinuria is the result of an underlying glomerulonephritis.

PRESENTATION AND DIAGNOSIS OF NEPHROTIC SYNDROME



OVERVIEW OF NEPHROTIC SYNDROME *(Continued)*

Once proteinuria is established, urine should be sent for protein quantification using a 24-hour urine collection or, for the sake of convenience, a spot urine protein:creatinine ratio. The latter offers a reasonable approximation of 24-hour proteinuria, especially if it is based on the first morning void.

Blood should be sent for measurement of albumin, cholesterol, electrolyte, and creatinine concentrations. Once laboratory tests reveal the triad of heavy proteinuria, hypoalbuminemia, and hypercholesterolemia, the patient clearly has nephrotic syndrome. The differential diagnosis at this point, therefore, is centered on determining the cause.

In children, MCD accounts for such an overwhelming majority of cases that treatment for this condition is offered on an empiric basis. Further workup, including renal biopsy, is not performed unless such treatment fails.

In adults, the differential diagnosis of nephrotic syndrome is broad enough to warrant a renal biopsy in cases where an apparent cause, such as long-standing diabetes mellitus, is not present. The histologic findings associated with each particular disease are described later in this section. In addition, adults should undergo screening for the most common causes of secondary nephrotic syndrome. For example, serologic testing should be performed for hepatitis B/C, HIV, lupus, and syphilis, and serum and urine protein electrophoresis should be performed to rule out amyloidosis and plasma cell disorders. Testing levels of serum complements (C3 and C4) can also be helpful because some causes of nephrotic syndrome are associated with depressed levels (e.g., membranoproliferative glomerulonephritis).

TREATMENT

The optimal treatment strategies depend on the underlying cause of nephrotic syndrome and are discussed later in this book. Some treatments, however, are useful in almost all patients.

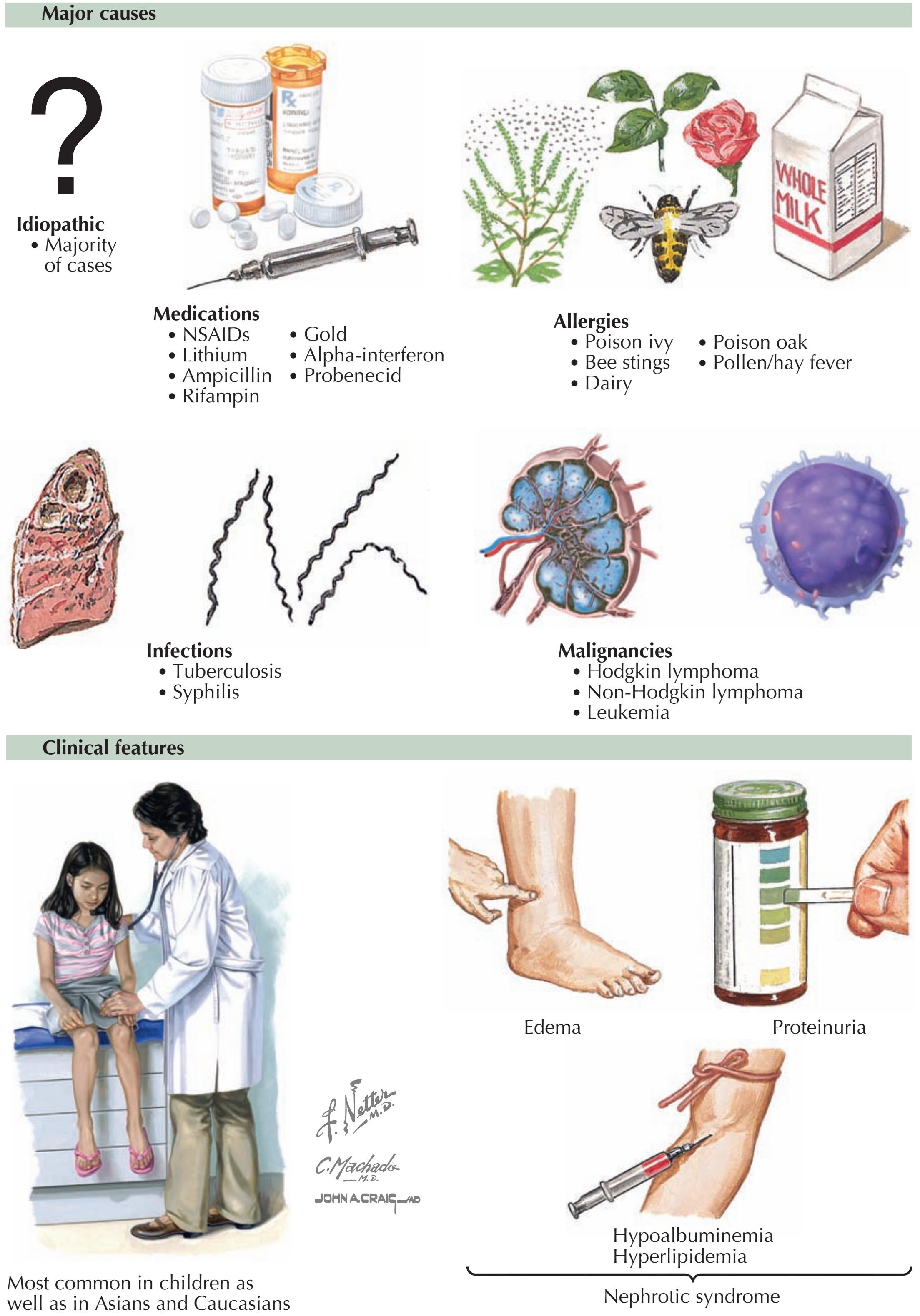
Renin-angiotensin system blockers (e.g., ACE inhibitors), for example, should be provided to all patients to lower blood pressure and reduce the degree of proteinuria. A cholesterol-lowering medication, such as a statin, should also be provided to minimize cardiovascular complications. Diuretics should be used as needed to treat edema; combinations of loop diuretics (e.g., furosemide), thiazides (e.g., chlorthalidone), and potassium-sparing diuretics (e.g., spironolactone) may be required. Anticoagulation may be necessary in patients who are at high risk for thrombosis or have already experienced a clotting event.

Many patients receive at least a short course of oral corticosteroids, although other immune-suppressing agents (such as calcineurin inhibitors, alkylating chemotherapy agents, and monoclonal antibodies) may also be used in certain circumstances.

Lifestyle changes are also important. Patients should adopt a low-salt diet to reduce edema and improve blood pressure control. Exercise may help mobilize edema and allow natural diuresis, as well as lower blood pressure and improve cholesterol levels.

Treatment success is defined as reduction or resolution of proteinuria, ideally to less than 300 mg/day, with preserved kidney function. Patients who achieve this endpoint generally have a very favorable prognosis. In contrast, those patients with nephrotic-range proteinuria that do not respond to treatment have a poor overall renal prognosis because ongoing glomerular inflammation will eventually lead to scarring and a permanent loss of renal function.

Causes and Presentation of Minimal Change Disease


Major causes
?
Idiopathic
• Majority of cases
Medications
• NSAIDs
• Lithium
• Ampicillin
• Rifampin
• Gold
• Alpha-interferon
• Probenecid
Allergies
• Poison ivy
• Bee stings
• Dairy
• Poison oak
• Pollen/hay fever
WHOLE MILK
Infections
• Tuberculosis
• Syphilis
Malignancies
• Hodgkin lymphoma
• Non-Hodgkin lymphoma
• Leukemia
Clinical features
Most common in children as well as in Asians and Caucasians
Edema
Proteinuria
Hypoalbuminemia
Hyperlipidemia
Nephrotic syndrome

MINIMAL CHANGE DISEASE

Minimal change disease (MCD, also known as nil disease and lipoid nephrosis) is the leading cause of nephrotic syndrome in children, accounting for 90% of cases in this population, and a major cause of nephrotic syndrome in adults. In addition to its predilection for children, MCD also occurs more frequently in Asians and Caucasians than in African-Americans.

The name of this disease refers to the seemingly normal appearance of glomeruli when visualized using light microscopy. On electron microscopy, however, diffuse foot process effacement can be seen, which is the basis for the proteinuria.

The vast majority (>85%) of MCD cases are primary, idiopathic phenomena. In the remaining cases, MCD occurs secondary to a systemic insult, such as drugs (e.g., NSAIDs, lithium), neoplasms (especially hematologic malignancies), infections (e.g., tuberculosis, syphilis), and allergies to common irritants (i.e., poison ivy, ragweed, poison oak, bee stings, certain foods).

PATHOPHYSIOLOGY

The precise mechanism of MCD is not known. One theory speculates that dysfunctional T-cells produce a cytokine called the glomerular permeability factor, which injures podocytes (visceral epithelial cells) and leads to foot process effacement. Loss of the slit diaphragm architecture, which constitutes the normal barrier to protein filtration, leads to proteinuria. B cells may also play a role, either by producing the glomerular permeability factor or, alternatively, by secreting an antibody that targets a glomerular antigen.

The immune-mediated hypothesis is supported by the efficacy of immunomodulatory treatments, as well as the fact that MCD may occur secondary to allergens, infections, and cancers of the immune system. In cases of idiopathic MCD, it is not clear what would trigger this abnormal immune response. Some have postulated that viral or bacterial infections may be responsible, although at present there is no evidence for this claim.

Despite the damage to podocytes, the remainder of the glomerulus remains normal. Thus renal function remains intact or is only slightly impaired.

PRESENTATION AND DIAGNOSIS

The most common presentation of MCD is the sudden onset of nephrotic syndrome (see Plate 4-7). Thus patients typically have substantial edema and the laboratory findings of nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia. In MCD, the proteinuria tends to be more profound than with other causes of nephrotic syndrome (e.g., > 10 to 15 g/day).

Serum markers of renal function, such as creatinine concentration, are typically normal or only slightly elevated. In a subset of adults, however, acute kidney injury may occur, possibly because of ischemic acute tubular necrosis resulting from massive loss of intravascular volume. For unclear reasons, adults are also more likely than children to have hypertension and hematuria.

Because patients with MCD tend to have very severe proteinuria, clinicians must be alert for the presence of related complications. As in all cases of nephrotic syndrome, patients are at risk for systemic thromboses. In addition, infection may occur because of multiple factors, including urinary losses of immunoglobulins, alternative complement factor B, and hemolytic factor D. If there is significant edema, the risk of cellulitis increases.

The gold standard for diagnosis of MCD is renal biopsy. In children, however, MCD accounts for such an overwhelming majority of nephrotic syndromes that it is often diagnosed on a presumptive basis, with renal biopsy not performed unless empiric treatment fails. In adults, the differential diagnosis for nephrotic syndrome is very broad, and thus in the absence of a clear

MINIMAL CHANGE DISEASE
(Continued)

underlying cause (such as long-standing diabetes mellitus), renal biopsy is essential for optimization of management.

On light microscopy, the glomeruli generally appear normal. Immunofluorescence is usually unremarkable, although occasional mesangial IgM or complement deposits may be seen. Further examination with electron microscopy, however, reveals diffuse foot process effacement. This finding is not pathognomonic for MCD, however, unless seen in the presence of normal light microscopy findings in an adequate sample size (typically at least 15 glomeruli).

It is important but sometimes challenging to distinguish MCD from FSGS. In some cases, patients diagnosed with MCD fail to respond to treatment and, on repeat biopsy, are found to have FSGS. It is not clear if these cases indicate missampled FSGS in the original biopsy, or a progression of MCD to FSGS due to prolonged periods of heavy proteinuria. Indeed, the relationship between these two entities is poorly understood and controversial; some experts believe that the two entities are on two ends of a continuum.

Once the diagnosis of MCD is established, patients should be screened for the major causes of secondary MCD. If all of these tests are negative or normal, the MCD can be ruled idiopathic.

TREATMENT

The primary, idiopathic form of MCD is very responsive to steroids. Up to 95% of patients achieve complete remission, defined as proteinuria declining to levels below 300 mg/day with stable renal function. Among children, half respond within 2 weeks of treatment, and nearly all of the others respond within 8 weeks. Among adults, half respond within 4 weeks of treatment, but the rest may require several months of additional corticosteroids. For as long as the nephrotic syndrome persists, all patients should adopt a low-salt diet, and diuretics should be used as needed for edema control. ACE inhibitors and statins are generally not required in steroid-responsive patients because their disease is short in duration.

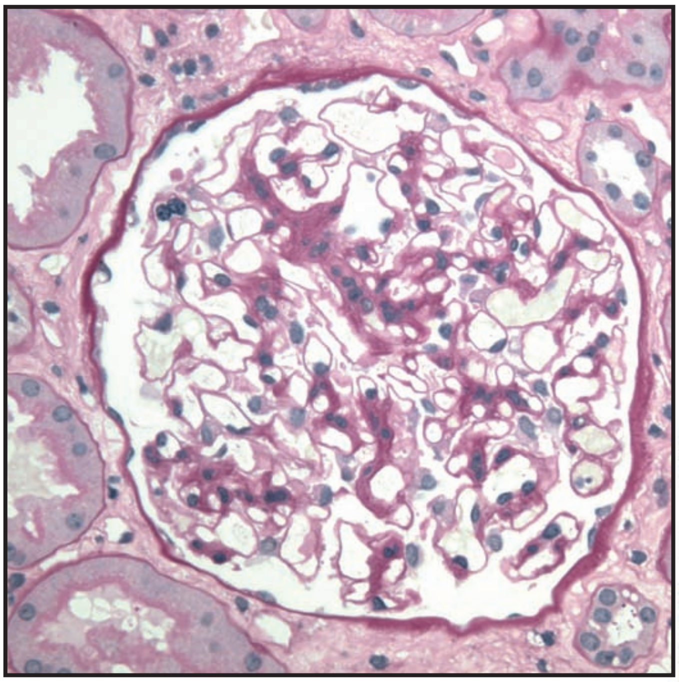
Secondary forms of MCD should be treated by focusing on removal or mitigation of the inciting insult, such as discontinuation of a certain drug or treatment of an underlying malignancy.

PROGNOSIS

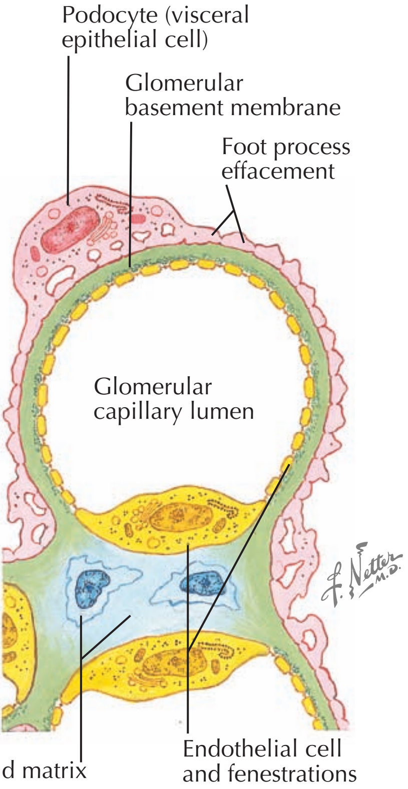
Patients who experience total remission have a very good long-term prognosis. In contrast, patients with disease that is unresponsive to treatment may experience progressive scarring of glomeruli, with an associated decline in renal function that ultimately leads to end-stage disease.

More than half of adult MCD patients will have a relapse during their lifetime, and up to one in four will become a frequent relapser, experiencing more than three episodes per year. In general, children and adults who go into remission quickly—sometimes within the first week of treatment—are less likely to have subsequent relapses. Because long-term use of steroids has numerous adverse effects, patients with relapsing disease are often prescribed alternative immunomodulatory therapies, such as calcineurin inhibitors, mycophenolate mofetil, and cyclophosphamide.

HISTOPATHOLOGIC FINDINGS OF MINIMAL CHANGE DISEASE

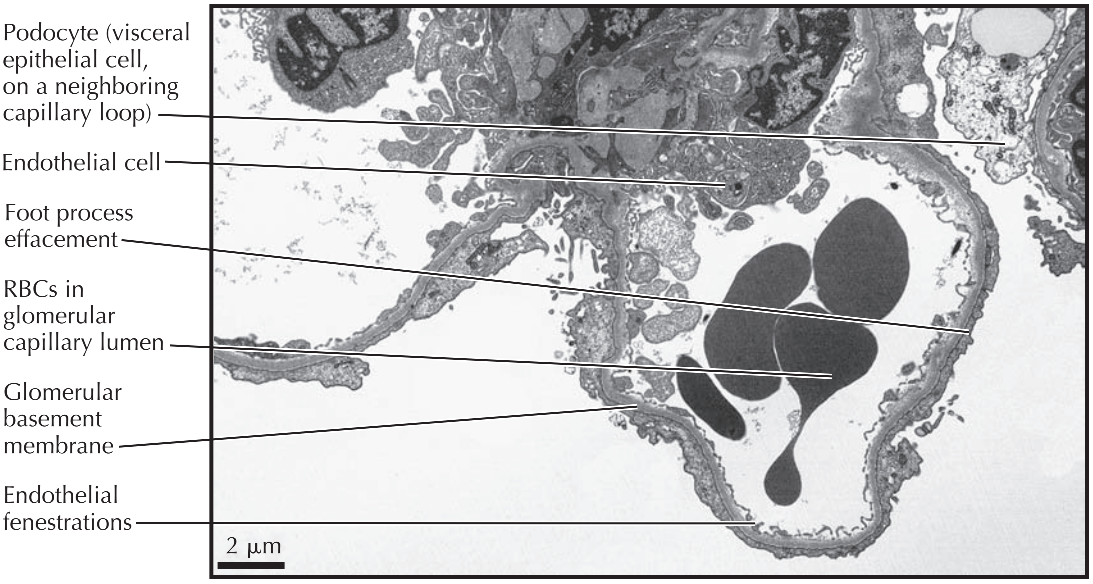


Light microscopy findings (PAS stain, 400 ×): Normal-appearing glomeruli, occasionally with slight increase in podocyte size



Schematic of electron microscopy findings

Podocyte (visceral epithelial cell)
Glomerular basement membrane
Foot process effacement
Glomerular capillary lumen
Mesangial cell and matrix
Endothelial cell and fenestrations

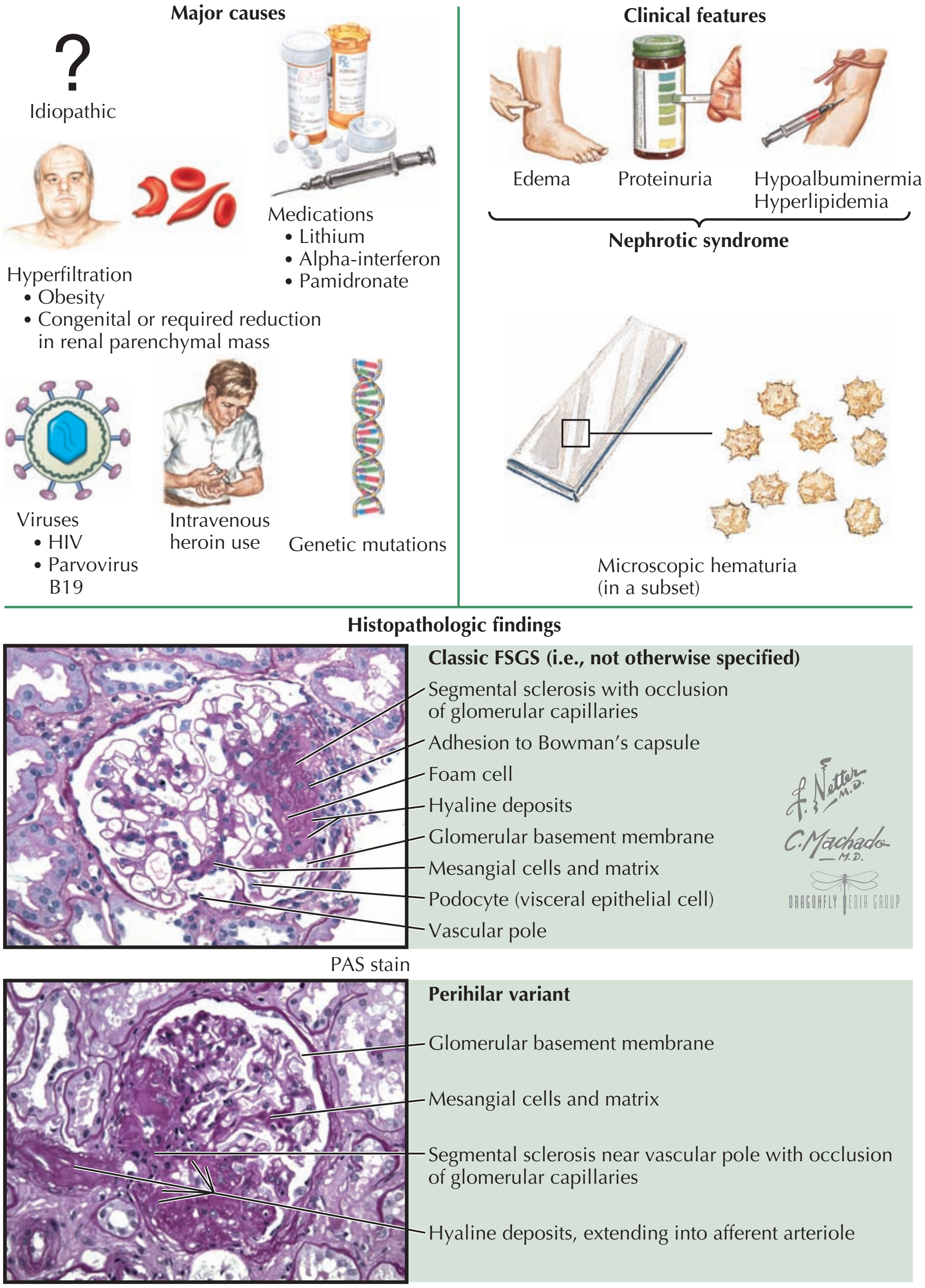


Podocyte (visceral epithelial cell, on a neighboring capillary loop)
Endothelial cell
Foot process effacement
RBCs in glomerular capillary lumen
Glomerular basement membrane
Endothelial fenestrations
2 µm

Electron microscopy findings (600 ×)

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

CAUSES, CLINICAL FEATURES, AND HISTOPATHOLOGIC FINDINGS OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS


Major causes
?
Idiopathic
Hyperfiltration
• Obesity
• Congenital or required reduction in renal parenchymal mass
Medications
• Lithium
• Alpha-interferon
• Pamidronate
Viruses
• HIV
• Parvovirus B19
Intravenous heroin use
Genetic mutations
Clinical features
Edema
Proteinuria
Hypoalbuminermia
Hyperlipidemia
Nephrotic syndrome
Microscopic hematuria (in a subset)
Histopathologic findings
Classic FSGS (i.e., not otherwise specified)
Segmental sclerosis with occlusion of glomerular capillaries
Adhesion to Bowman's capsule
Foam cell
Hyaline deposits
Glomerular basement membrane
Mesangial cells and matrix
Podocyte (visceral epithelial cell)
Vascular pole
PAS stain
F. Netter M.D.
C. Machado M.D.
DRAGONFLY MEDIA GROUP
Perihilar variant
Glomerular basement membrane
Mesangial cells and matrix
Segmental sclerosis near vascular pole with occlusion of glomerular capillaries
Hyaline deposits, extending into afferent arteriole
PAS stain

Focal segmental glomerulosclerosis (FSGS) is a clinical-pathologic syndrome in which there is proteinuria accompanied by glomerular scarring or sclerosis that occurs in a focal (i.e., subset of all glomeruli) and segmental (i.e., portion of each affected glomerulus) distribution. FSGS is a major cause of nephrotic syndrome in adults, and it can occur as a primary, idiopathic process or secondary to numerous systemic conditions, including viruses (HIV, parvovirus B19), medications (pamidronate, lithium, alpha interferon), inherited genetic diseases (mutations in podocyte proteins such as α-actinin-4 or podocin), heroin abuse, and any disorder that causes glomerular hyperfiltration (such as morbid obesity or any congenital or acquired reduction in renal parenchymal mass, including renal agenesis, renal dysplasia, renal ablation, diabetic nephropathy, sickle cell anemia, or any advanced chronic kidney disease).

In the United States, FSGS is responsible for more cases of end-stage renal disease (ESRD) than any other primary glomerular disease. Its incidence has increased over past decades, for unknown reasons. It is more common in African Americans than Caucasians, possibly because of inherited genetic factors.

PATHOPHYSIOLOGY

The pathogenesis of FSGS is poorly understood. In primary, idiopathic disease, it appears that a circulating permeability factor is responsible, a hypothesis supported by the fact that FSGS can rapidly recur in a transplanted allograft. Although the exact nature of the glomerular injury remains unknown, it appears probable that podocytes (visceral epithelial cells) are a major target, and that injury or loss of these cells leads to proteinuria and sclerosis.

The pathogenetic bases of secondary FSGS are likely diverse. In HIV-associated FSGS, for example, the virus is thought to directly infect podocytes and disrupt normal regulatory patterns. In hyperfiltration states, increased glomerular pressure is thought to cause progressive endothelial and podocyte injury, ultimately leading to FSGS.

PRESENTATION AND DIAGNOSIS

All patients with FSGS have some degree of proteinuria, which may cause the nephrotic syndrome if severe (see Plate 4-7). On quantification with a 24-hour collection or spot urine protein : creatinine ratio, the proteinuria may vary from less than 1 to more than 10 g/day. A subset of patients will also be found to have hematuria. Laboratory evaluation of serum may reveal hypoalbuminemia and hypercholesterolemia if the proteinuria is in the nephrotic range. A subset of patients will have renal insufficiency, manifest as an elevated serum creatinine concentration.

The specific diagnosis of FSGS can only be established based on histopathologic findings. Renal biopsy should be performed in adults with nephrotic syndrome in the absence of an apparent cause (i.e., long-standing diabetes mellitus), or in children with unexplained nephrotic syndrome who do not respond to empiric treatment for MCD (see Plate 4-8).

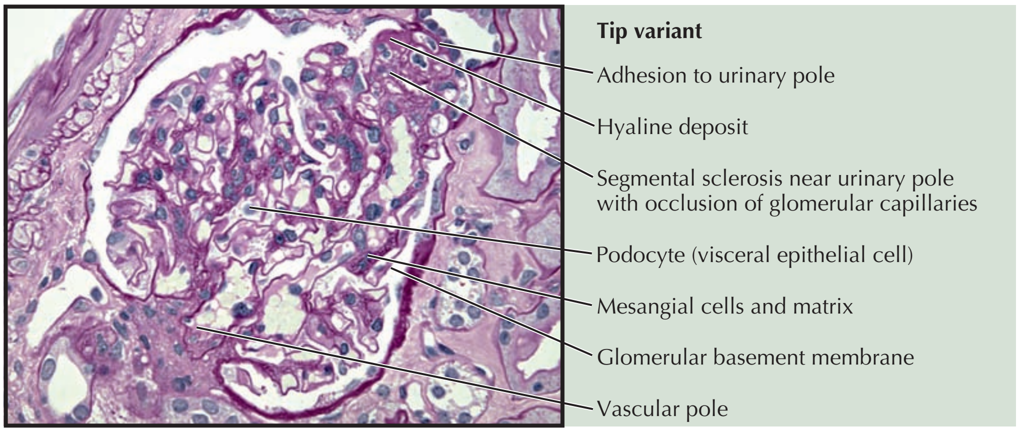
Using light microscopy, glomerulosclerosis is seen in a focal and segmental distribution. Segmental occlusion of glomerular capillaries occurs as the end result of several pathologic changes, including hyalinosis (glasslike deposits resulting from subendothelial accumulation of plasma proteins), podocyte swelling, and accumulation of extracellular matrix. Foam cells may be seen trapped within the capillaries of the sclerotic segments. In addition, segmental adhesions may be seen between the sclerotic portions of the glomerular tuft and the adjacent lining of Bowman's capsule.

Several histologic variants of FSGS can be distinguished, including classic FSGS (also known as FSGS not otherwise specified), perihilar variant, glomerular tip variant, cellular variant, and collapsing variant. It is unclear if these different subtypes have different pathophysiologic bases or merely represent different degrees of glomerular damage.

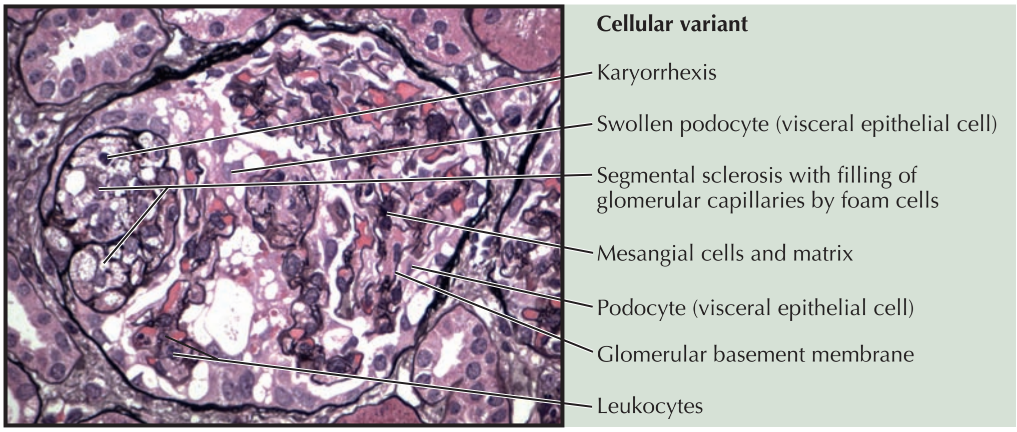
The perihilar variant of FSGS is characterized by the presence of perihilar hyalinosis and sclerosis in >50% of affected glomeruli. This variant can be seen in primary disease; however, if seen in the presence of glomerulomegaly, it suggests a secondary form related to glomerular hyperfiltration. The glomerular tip variant is characterized by a focal lesion localized near the urinary pole of Bowman's capsule, where the proximal tubule begins. The capillary lumina in this region appear obliterated secondary to the presence of foam cells and swollen endothelial cells, whereas the overlying podocytes appear hypertrophic and confluent with adjacent parietal and tubular epithelial cells. Adhesions may be seen between the glomerular tuft and the

FOCAL SEGMENTAL GLOMERULOSCLEROSIS *(Continued)*

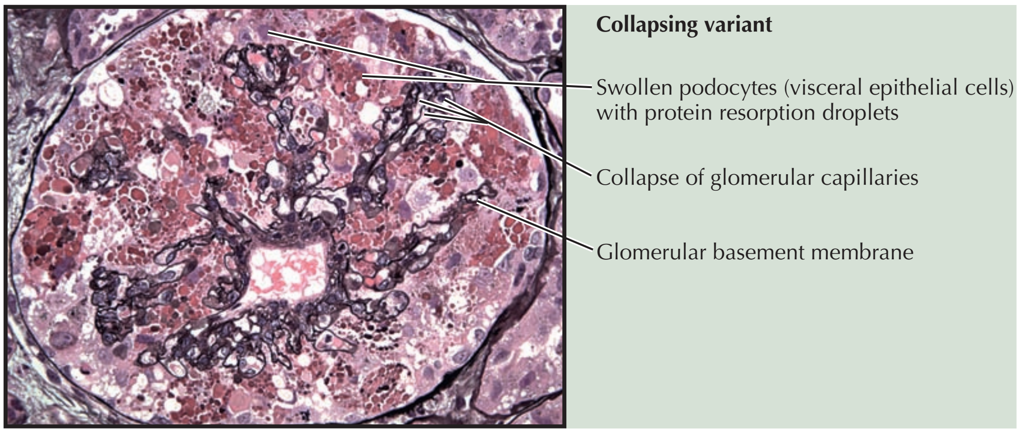
HISTOPATHOLOGIC FINDINGS OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS (CONTINUED)


Tip variant
Adhesion to urinary pole
Hyaline deposit
Segmental sclerosis near urinary pole with occlusion of glomerular capillaries
Podocyte (visceral epithelial cell)
Mesangial cells and matrix
Glomerular basement membrane
Vascular pole

PAS stain


Cellular variant
Karyorrhexis
Swollen podocyte (visceral epithelial cell)
Segmental sclerosis with filling of glomerular capillaries by foam cells
Mesangial cells and matrix
Podocyte (visceral epithelial cell)
Glomerular basement membrane
Leukocytes

Silver stain


Collapsing variant
Swollen podocytes (visceral epithelial cells) with protein resorption droplets
Collapse of glomerular capillaries
Glomerular basement membrane

Silver stain

urinary pole. The cellular variant is characterized by the presence of segmental endocapillary hypercellularity in at least one glomerulus that affects at least 25% of the tuft and results in occlusion of the capillary lumina. The infiltration of leukocytes, foam cells, and other cell types may result in karyorrhexis and other evidence of active inflammation. The collapsing variant is characterized by a segmental or global collapse of glomerular capillaries with significant hypertrophy and hyperplasia of overlying podocytes, which often contain large intracytoplasmic protein resorption droplets. Unlike in other FSGS variants, hyalinosis and foam cells are generally not seen. This variant may occur as a primary phenomenon but is also the characteristic lesion of HIV-associated nephropathy (see Plate 4-55).

On immunofluorescence, all types may reveal irregular positive staining for immunoglobulin M and complement factor C3 in the same focal, segmental distribution as the glomerulosclerosis. Strongly positive staining for antibodies or complement proteins in nonsclerotic glomeruli suggests an underlying immune complex glomerulonephritis. Electron microscopy of the sclerotic lesions in all subtypes reveals wrinkling and retraction of the glomerular basement membrane (GBM), subendothelial accumulation of hyaline material, diffuse foot process effacement, podocyte hypertrophy, and focal areas of podocyte detachment from the GBM.

If FSGS is diagnosed, patients should be screened for secondary causes that may otherwise be subclinical, such as HIV infection.

TREATMENT

All patients with FSGS (both primary and secondary forms) should receive angiotensin-converting enzyme (ACE) inhibitors or aldosterone receptor blockers (ARBs) to reduce proteinuria and slow the progression to end-stage renal disease (ESRD). Hyperlipidemia, if present, should be treated with a cholesterol-lowering medication, such as a statin. Patients with edema may require diuretic therapy and should be encouraged to adopt a low-salt diet. Blood pressure should be aggressively controlled.

In cases of primary FSGS with subnephrotic proteinuria, the above conservative measures are often adequate. In cases with nephrotic syndrome, immunosuppression is warranted. Initial treatment is with high dose glucocorticoids for up to 6 months. About half of patients attain either full remission (<300 mg/day of proteinuria) or partial remission (reduction in nephrotic rage proteinuria by > 50%) with glucocorticoids. For those patients who do not achieve remission, or who experience relapsing disease, cyclosporine or tacrolimus (both calcineurin inhibitors) can be used as second line agents as long as renal function is relatively intact.

In cases of secondary FSGS, treatment should focus on reversing the underlying cause, which may slow down or halt progression of the renal disease.

PROGNOSIS

Overall, idiopathic FSGS has a significantly higher rate of progression to ESRD than secondary forms. The clinical features that portend a poor prognosis include high levels of proteinuria (particularly if associated with nephrotic syndrome), impaired renal function, and failure to achieve remission (either complete or partial). The pathologic features that portend a poor prognosis include collapsing variant and high levels of interstitial fibrosis. In contrast, the glomerular tip variant confers a more favorable prognosis, with a higher likelihood of attaining disease remission with steroids.

If appropriate treatment is not provided, a significant portion of patients with primary FSGS will progress to ESRD. Only a small minority of patients experience complete spontaneous remission. Patients who progress to end-stage renal disease and receive a renal transplant are at risk for recurrent FSGS in the allograft.

C1Q NEPHROPATHY

C1q nephropathy is a rare but distinct cause of nephrotic syndrome with a clinical presentation and histopathologic findings that are very similar to what is seen with FSGS. Like FSGS, C1q nephropathy is also more common among African Americans. The pathogenesis is unknown but is likely immune-mediated. The major feature that distinguishes C1q nephropathy from FSGS is the presence of mesangial immune complex deposits that stain positive for C1q on immunofluorescence. Staining is often positive for IgG, IgM, and C3 as well. There is no established treatment for C1q nephropathy. Some clinicians advise steroids, although the literature has offered mixed results regarding its efficacy.

MEMBRANOUS NEPHROPATHY

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. It is named for the major histologic finding of diffuse glomerular basement membrane (GBM) thickening. The epidemiology and overall incidence of this disease has remained constant over several decades, with a peak incidence between 30 and 50 years of age.

In most cases MN is a primary phenomenon. About one quarter of cases, however, occur secondary to systemic diseases or infections. The major causes include systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren syndrome, Hashimoto thyroiditis, viral hepatitis infection (hepatitis B and, less commonly, hepatitis C), hematopoietic stem cell transplantation, and solid tumors (e.g., lung, colon, breast, kidney carcinomas). Some medications—such as gold, penicillamine, NSAIDs, and antitumor necrosis factor agents—have also been implicated.

PATHOPHYSIOLOGY

Primary MN occurs when circulating antibodies permeate the GBM and form immune complexes with epitopes on podocyte membranes. Although lymphocytes do not have access to this space, formation of complement C5b-C9 membrane attack complexes inflicts significant damage on podocytes. As a result, foot process effacement occurs, and the glomerular capillary walls are no longer capable of excluding proteins from the urinary space. In addition, the damaged podocytes secrete additional extracellular material that leads to expansion of the GBM.

For several decades, the specific podocyte epitope responsible for the above processes was unknown. During this time, however, it was discovered that antibodies targeting megalin, a podocyte membrane protein, produced a nearly identical disease in rats known as Heymann nephritis. Although this finding offered insights into the basic mechanism for MN, it did not clarify the relevant epitope in humans because megalin is not expressed on human podocytes.

More recent research, however, identified the M-type phospholipase A2 receptor (PLA2R), found on the surface of podocytes, as a major antigen in primary MN. In one series, antibodies targeting this transmembrane protein were identified in approximately 70% of patients with primary MN. In contrast, these antibodies were not identified in patients with secondary MN or healthy controls.

Secondary MN appears to result from subepithelial deposits of circulating immune complexes. Presumably, the antigens involved in the various disease states that cause secondary MN—double-stranded DNA in SLE; hepatitis B antigen; carcinoembryonic antigen, prostate specific antigen, and many others in malignancy; thyroglobulin in thyroiditis; treponemal antigen, and many others in syphilis—spur formation of immune complexes, which deposit in the glomerulus. In secondary MN these immune complexes are found in the subepithelial space, which leads to podocyte injury. Unlike in primary MN, however, immune complexes may also deposit in the mesangium and extraglomerular sites.

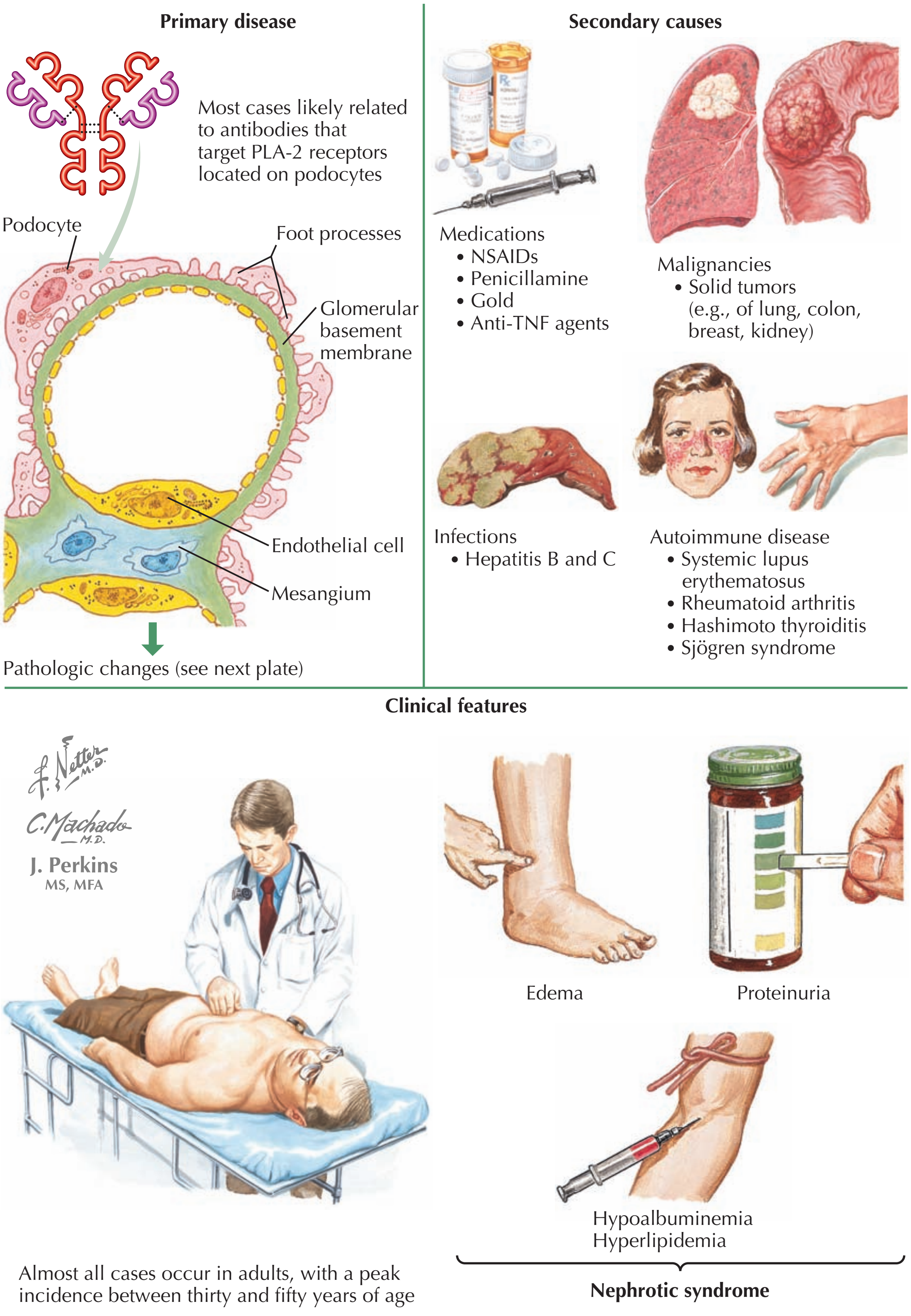
PRESENTATION AND DIAGNOSIS

The classic presentation of MN is nephrotic syndrome (see Plate 4-7) with an insidious onset. Patients typically describe slowly progressive lower extremity edema that, in some cases, has advanced to overt anasarca. Laboratory examination of serum and urine reveals proteinuria, hypoalbuminemia, and hyperlipidemia. Renal function, as inferred from serum creatinine concentration, is usually intact. The degree of proteinuria in MN patients is variable, ranging from subnephrotic (i.e., less than 3.5 g/day) to more than 20 g/day. Some patients may have completely asymptomatic proteinuria.

Patients with MN are at increased risk of renal vein thrombosis, even among other patients with nephrotic syndrome. This complication affects up to one in five patients in some series. In general, the heavier the proteinuria and lower the serum albumin, the higher the risk for thrombotic complications.

MN can only be diagnosed based on histopathologic findings. Thus in adults with unexplained nephrotic syndrome, renal biopsy must be performed. In MN,

CAUSES AND CLINICAL FEATURES OF MEMBRANOUS NEPHROPATHY


Primary disease
Secondary causes
Most cases likely related to antibodies that target PLA-2 receptors located on podocytes
Podocyte
Foot processes
Glomerular basement membrane
Endothelial cell
Mesangium
Pathologic changes (see next plate)
Medications
• NSAIDs
• Penicillamine
• Gold
• Anti-TNF agents
Malignancies
• Solid tumors (e.g., of lung, colon, breast, kidney)
Infections
• Hepatitis B and C
Autoimmune disease
• Systemic lupus erythematosus
• Rheumatoid arthritis
• Hashimoto thyroiditis
• Sjögren syndrome
Clinical features
F. Netter M.D.
C. Machado M.D.
J. Perkins MS, MFA
Edema
Proteinuria
Hypoalbuminemia
Hyperlipidemia
Almost all cases occur in adults, with a peak incidence between thirty and fifty years of age
Nephrotic syndrome

MEMBRANOUS NEPHROPATHY
(Continued)

light microscopy reveals diffuse GBM thickening, which is especially prominent with silver stains. The pathogenetic immune complexes are not visible at this resolution; however, the growing GBM forms “spikes” between these complexes, which may be seen instead. In primary MN there are generally no cellular infiltrates, since the immune complexes form in the subepithelium and are thus protected from the circulation. In secondary MN, however, infiltrates may occur because circulating immune complexes also deposit in the mesangium.

Immunofluorescence reveals diffuse granular staining for IgG and C3 along the GBM. Using electron microscopy, effacement of podocyte foot processes may be seen. In addition, the subepithelial immune complexes are visible as electron-dense deposits. These are limited to the subepithelium in primary MN but may also be visible in the mesangium in secondary disease. The presence of endothelial tubulo-reticular inclusions suggests SLE-related disease.

If biopsy confirms MN, patients should be evaluated for the most common causes of secondary disease, especially if there are also suggestive histologic findings. The most important laboratory tests include antinuclear and anti-dsDNA antibodies for SLE; hepatitis B and C serologies; and rapid plasma reagin screening for syphilis. In addition, all patients above the age of 40 with confirmed MN should undergo screening for malignancies because the incidence is about 5% to 10% in this population, rising as high as 20% in patients over 60 years old. Even patients with a negative initial workup should continue to undergo surveillance because malignancies may not appear until months or even years after the onset of nephrotic syndrome.

TREATMENT

All patients should be placed on a renin-angiotensin system blocker (e.g., ACE inhibitor) and cholesterol-lowering medication, such as a statin, for as long as the proteinuria continues. Edema can be treated as needed with diuretic therapy, and all patients should be encouraged to adopt a low-salt diet.

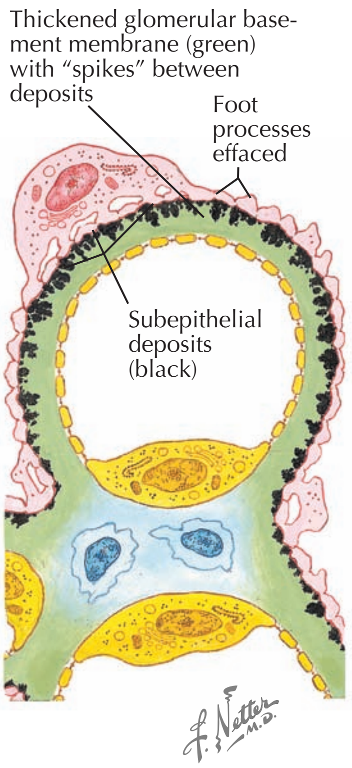
In idiopathic MN, the need for immunosuppression depends on the risk of disease progression. Patients with subnephrotic proteinuria, for example, often experience spontaneous remission and should therefore receive only the conservative treatments listed above.

Patients with very heavy proteinuria (more than 8 to 9 g/day), in contrast, will likely develop progressive chronic kidney disease if they do not receive immunosuppressive agents. Patients with intermediary proteinuria (between 3.5 to 8 g/day) should receive immunosuppressive agents if proteinuria does not fall below 3.5 g/day after 6 months of conservative management.

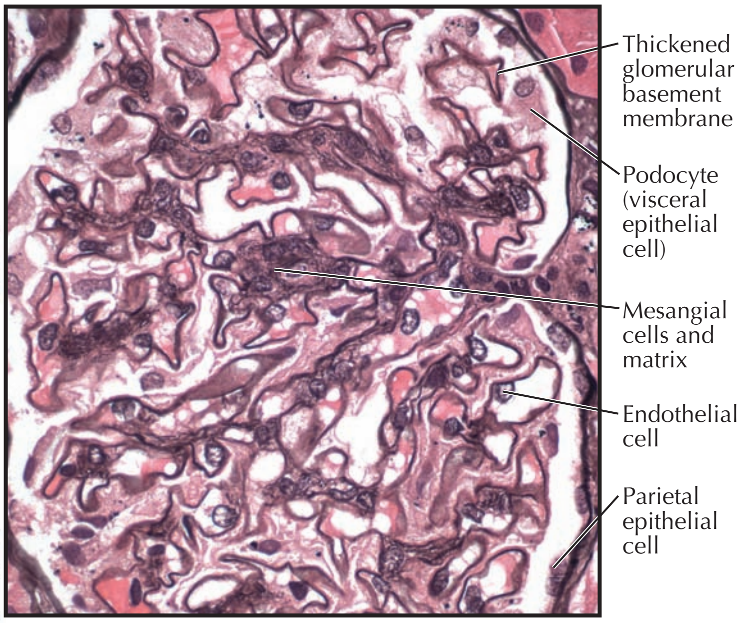
Several immunosuppressive agents may be used to treat primary MN. The two leading therapies are alkylating agents (cyclophosphamide or chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus), either of which is given in combination with oral or intravenous corticosteroids. Recently, other agents such as rituximab, ACTH, and mycophenolate mofetil have also shown promising results, particularly in cases refractory to initial therapeutic attempts.

HISTOPATHOLOGIC FINDINGS OF MEMBRANOUS NEPHROPATHY

Schematic

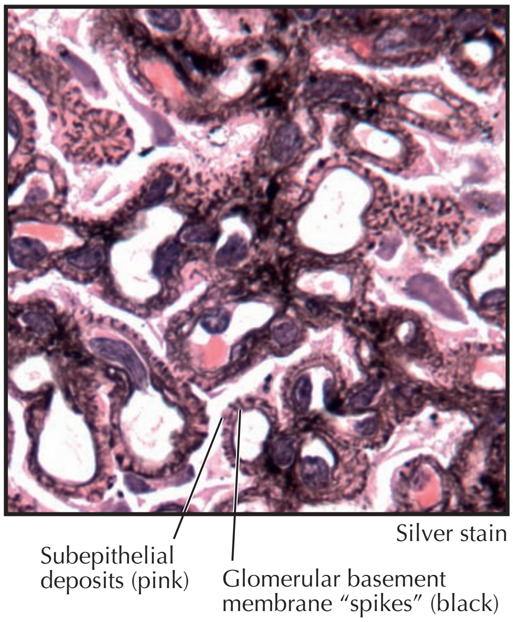

Thickened glomerular basement membrane (green) with “spikes” between deposits
Foot processes effaced
Subepithelial deposits (black)
F. Netter M.D.

Low-power light microscopy


Thickened glomerular basement membrane
Podocyte (visceral epithelial cell)
Mesangial cells and matrix
Endothelial cell
Parietal epithelial cell

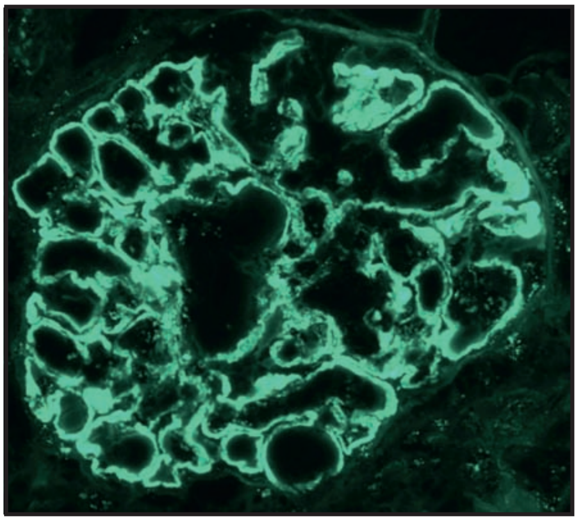
Silver stain

High-power light microscopy


Subepithelial deposits (pink)
Glomerular basement membrane “spikes” (black)

Silver stain

Immunofluorescence



Granular staining of capillary walls seen on anti-IgG immunofluorescence, consistent with immune complex deposition/formation

In secondary MN, treatment centers on removal of the underlying cause, after which there is often a complete remission of proteinuria within several months.

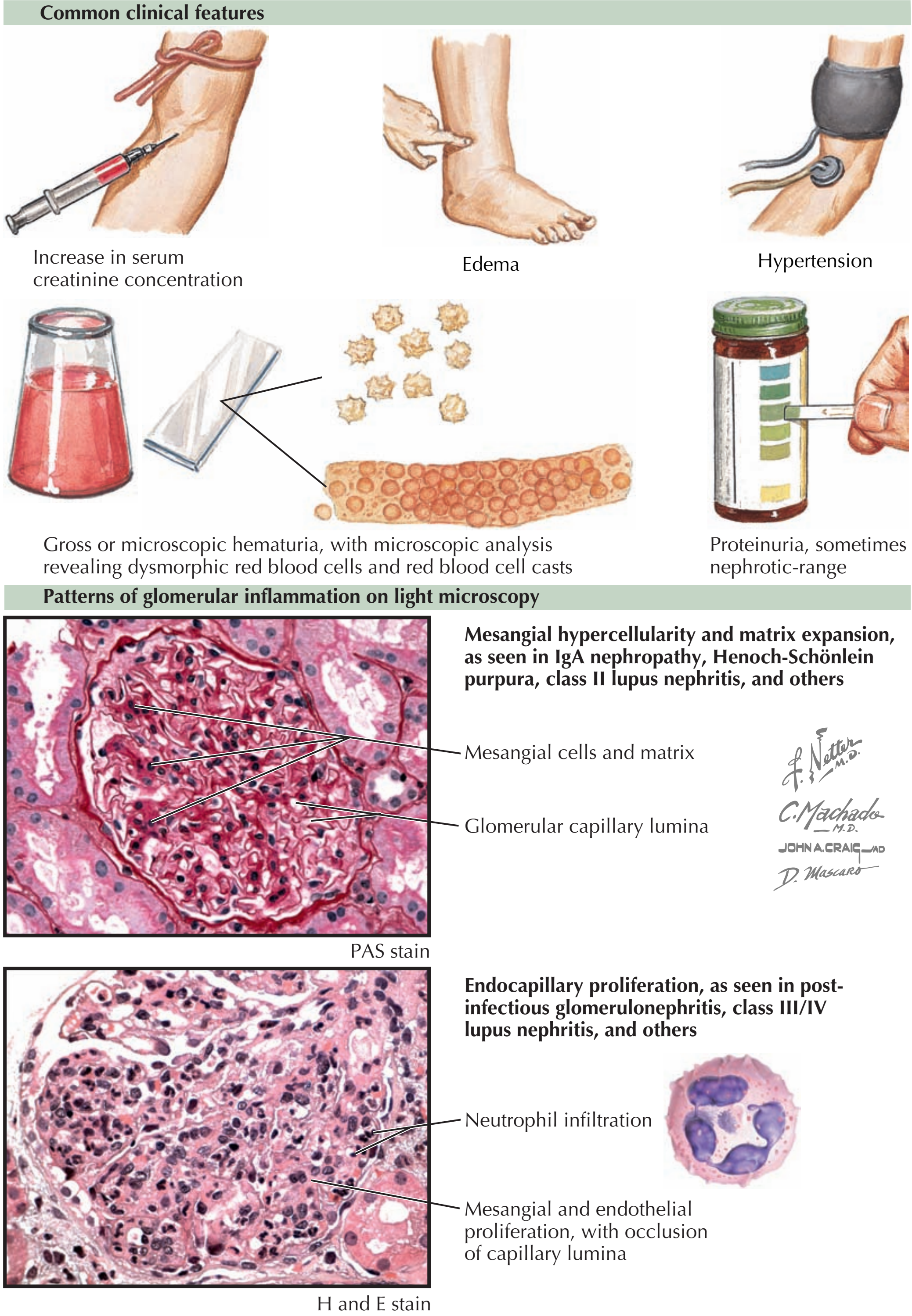
PROGNOSIS

Patients with idiopathic MN who experience either spontaneous or drug-induced remission have an excellent prognosis, and the majority of patients who receive immunosuppression achieve complete or partial remission. Relapse, however, occurs in up to 30%, requiring repeat rounds of immunosuppression.

The patients who do not achieve long-term remission may experience a progressive, sometimes rapid, decline in renal function that can progress to ESRD. If a transplant is performed, the risk of MN recurring in the allograft is approximately 10% to 15%.

OVERVIEW OF GLOMERULONEPHRITIS

CLINICAL FEATURES AND HISTOPATHOLOGIC FINDINGS OF GLOMERULONEPHRITIS


Common clinical features
Increase in serum creatinine concentration
Edema
Hypertension
Gross or microscopic hematuria, with microscopic analysis revealing dysmorphic red blood cells and red blood cell casts
Proteinuria, sometimes nephrotic-range
Patterns of glomerular inflammation on light microscopy
Mesangial hypercellularity and matrix expansion, as seen in IgA nephropathy, Henoch-Schönlein purpura, class II lupus nephritis, and others
Mesangial cells and matrix
Glomerular capillary lumina
PAS stain
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Endocapillary proliferation, as seen in post-infectious glomerulonephritis, class III/IV lupus nephritis, and others
Neutrophil infiltration
Mesangial and endothelial proliferation, with occlusion of capillary lumina
H and E stain

Glomerulonephritis (GN) is a general term used to indicate glomerular inflammation, which may occur secondary to many different disease processes. The specific pattern of inflammation, as dictated by the underlying process, generally determines the major signs and symptoms, which may include microscopic or gross hematuria, proteinuria, hypertension, edema, and/or renal insufficiency.

PRESENTATION

Glomerulonephritis may present as any of the following clinical syndromes:

Asymptomatic Hematuria with or Without Proteinuria. Adults with IgA nephropathy (see Plate 4-16) often present in this manner. Their urinary abnormalities are commonly discovered on routine physical examination and urine dipstick.

Recurrent Gross Hematuria. Children with IgA nephropathy often present in this manner, developing gross hematuria several days after an upper respiratory infection (“synpharyngitic nephritis”).

Acute GN. Patients have “nephritic syndrome,” which includes variable degrees of renal insufficiency; oliguria; hypertension; edema; proteinuria; and gross or microscopic hematuria. Poststreptococcal GN (Plate 4-19), membranoproliferative GN (Plate 4-22), and lupus nephritis (Plate 4-49) often present in this manner.

Rapidly Progressive Glomerulonephritis (RPGN). Patients experience a rapid deterioration of renal function over days, weeks, or months that invariably progresses to end-stage renal disease (ESRD) if untreated. Any form of glomerulonephritis may cause RPGN, although vasculitic glomerulonephritis and antiglomerular basement membrane disease frequently cause this severe phenotype.

Chronic GN. Patients have minimal symptoms and are often discovered to have hypertension, renal impairment, and proteinuria on routine physical examination and laboratory assessment. IgA nephropathy frequently presents in this manner after years of preceding asymptomatic hematuria/proteinuria, which may have gone unnoticed.

DIAGNOSIS

Glomerulonephritis should be suspected in any patient with one of the above clinical presentations. Proteinuria should be quantified using either a 24-hour collection or, more often, a spot urine protein : creatinine ratio. Glomerular hematuria can be distinguished from other causes of urinary tract bleeding by the presence of either dysmorphic red blood cells (RBCs) or RBC casts on urine microscopy. RBCs become dysmorphic upon passing through the damaged GBM. An acanthocyte, characterized by its protruding blebs, is an example of a dysmorphic RBC. A large number of dysmorphic RBCs (often defined as 50% to 80% of RBCs seen on urine microscopy) indicates glomerular bleeding. Meanwhile, some of the RBCs in the tubules become bound together by the Tamm-Horsfall mucoprotein, forming RBC casts, which are thus also characteristic of glomerular bleeding.

The different causes of glomerulonephritis are distinguished based on history, clinical findings, serologic tests, and renal biopsy findings. The characteristic features of each disease process are described later in this section. Some general terms, however, are often used to describe the patterns of glomerular inflammation seen on light microscopy and immunofluorescence.

Light Microscopy

With light microscopy, the pattern of glomerular inflammation is often described as mesangial, endocapillary, and/or extracapillary (crescentic); focal or diffuse; and segmental or global.

Mesangial/Endocapillary/Extracapillary (Crescentic). Inflammation can occur in several different regions of the glomerulus, leading to characteristic structural changes.

Mesangial involvement can manifest as mesangial hypercellularity (defined as more than three mesangial cells per mesangial area) and/or mesangial matrix expansion. These structural changes are often associated with microscopic hematuria and/or mild proteinuria, with preservation of normal filtration function. Common causes include IgA nephropathy and class II lupus nephritis.

Endocapillary involvement can manifest as occlusion of glomerular capillaries by endothelial and mesangial cell proliferation, as well as by leukocyte infiltration. These changes are often associated with hematuria, proteinuria, and reduction of filtration function.

OVERVIEW OF GLOMERULONEPHRITIS *(Continued)*

Common causes include postinfectious GN and class III or IV lupus nephritis.

Extracapillary involvement, more commonly known as crescentic disease, manifests as thickening of the parietal epithelium of Bowman's capsule to more than two cell layers, which causes it to resemble a crescent. The formation of such crescents occurs secondary to the rupture of glomerular capillaries, which permits cells and proteins to leak into and accumulate along Bowman's space. Cellular crescents are the defining lesion of rapidly-progressive glomerulonephritis (RPGN, see Plate 4-25).

Focal/Diffuse. In focal GN, fewer than half of the glomeruli appear abnormal. Common causes of focal disease include IgA nephropathy and class III lupus nephritis.

In diffuse GN, more than half of the glomeruli appear abnormal. Common causes include postinfectious GN, class IV lupus nephritis, and membranoproliferative GN.

Segmental/Global. In segmental lesions, fewer than half of the capillaries within most affected glomerular tufts appear abnormal. In global lesions, more than half of the capillaries within most affected glomerular tufts appear abnormal.

Immunofluorescence

The pattern observed on immunofluorescent staining of the glomerulus for antibodies and/or complement proteins can often be described as granular, linear, or pauci-immune. These patterns offer clues into the underlying disease process.

Granular. A pattern of patchy, granular staining for antibodies and complement proteins suggests immune complex deposition. The deposited complexes fix complement, leading to direct complement-mediated damage and, frequently, endocapillary proliferation.

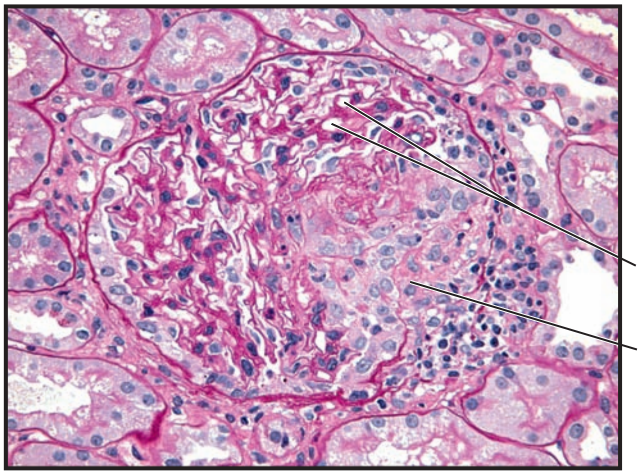
IgA nephropathy is the most common cause of immune complex GN and the most common cause of GN in general. Other causes of immune complex GN include lupus nephritis, membranoproliferative GN, and postinfectious GN. These diseases are typically associated with depressed complement levels, reflecting their mechanism of inflammation; however, complement levels may remain normal in IgA nephropathy because of the slow rate at which the various components are consumed.

Linear. A pattern of continuous, linear staining for antibodies and complement proteins along the capillary walls suggests direct binding of antibodies to the glomerular basement membrane (GBM). Such binding occurs in the anti-GBM diseases, in which autoantibodies form against the noncollagenous 1 (NC1) domain of the α-3 chain of type IV collagen (α-3 IV). The resulting inflammation almost invariably leads to RPGN.

In the spectrum of anti-GBM disease, one third of patients have renal-limited disease, whereas the remainder have the combined pulmonary-renal syndrome named for Goodpasture. Goodpasture syndrome occurs when the anti-GBM autoantibodies bind to the alveolar basement membrane, causing pulmonary hemorrhage. This syndrome occurs almost exclusively in smokers and others exposed to hydrocarbons, suggesting that environmental factors play a key role in determining the susceptibility of the pulmonary capillaries to circulating anti-GBM autoantibodies.

HISTOPATHOLOGIC FINDINGS OF GLOMERULONEPHRITIS (CONTINUED)

Patterns of glomerular inflammation on light microscopy (continued)



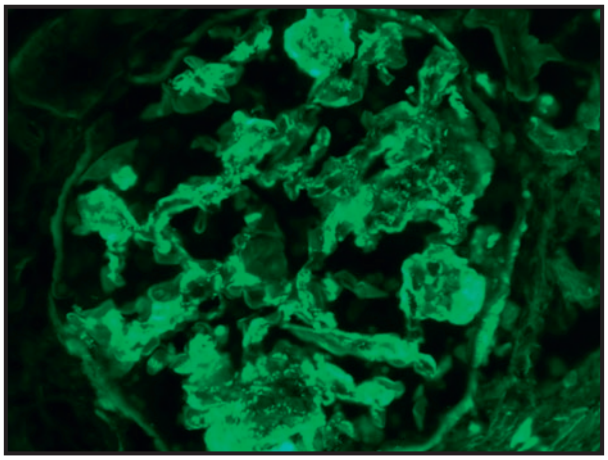
Extracapillary (crescentic) proliferation, as seen in various vasculitides, anti-GBM disease, and severe cases of IgA nephropathy, Henoch-Schönlein purpura, membranoproliferative glomerulonephritis, class III/IV lupus nephritis, and other immune complex glomerulonephritides

Glomerular capillary lumina

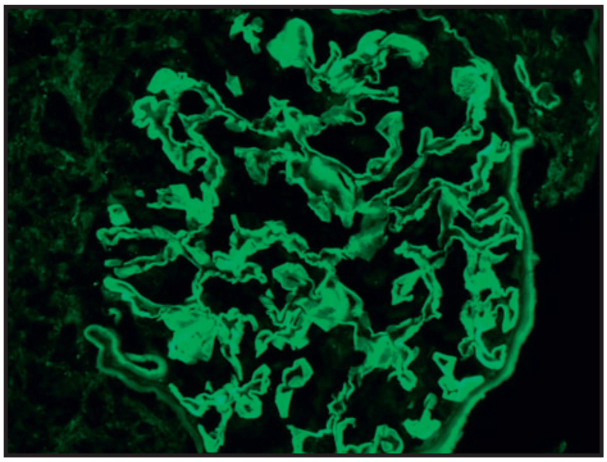
Accumulation of cells in Bowman's space, secondary to rupture of glomerular basement membrane, forms cellular crescent

PAS stain

Patterns of glomerular inflammation on immunofluorescence



Granular staining for antibodies, as seen in immune-complex diseases such as IgA nephropathy, post-infectious glomerulonephritis, membranoproliferative glomerulonephritis, and lupus nephritis



Linear staining for antibodies, as seen in anti-GBM disease (either isolated or as part of Goodpasture syndrome)

Pauci-immune. A general lack (or, as the name suggests, paucity) of staining for antibodies or complement proteins suggests vasculitic GN. In such cases, inflammation generally reflects the presence of circulating antineutrophil cytoplasmic antibodies (ANCAs), which are believed to directly activate neutrophils. The ensuing glomerular inflammation often leads to RPGN, and it may be either isolated or part of a systemic vasculitis. Other common histologic findings include fibrinoid glomerular necrosis, periglomerular inflammation, and arteritis.

ANCAs can be subdivided into those with a cytoplasmic staining pattern (c-ANCA) and those with a perinuclear staining pattern (p-ANCA). c-ANCAs almost always target proteinase-3 antigens (PR3-ANCA) and are often associated with Wegener granulomatosis. p-ANCAs almost always target myeloperoxidase antigens (MPO-ANCA) and are often associated with Churg-Strauss disease and microscopic polyangiitis. The ANCA-positive systemic vasculitides all feature a propensity toward multiple organ involvement. Specifically, Wegener granulomatosis and microscopic polyangiitis are associated with pulmonary hemorrhage, whereas Churg-Strauss features asthma and eosinophilia.

IGA NEPHROPATHY

IgA nephropathy (IgAN; also known as Berger disease) is the most common primary glomerular disease worldwide. IgAN can occur as a primary renal phenomenon or secondary to various extrarenal conditions, including chronic hepatic disease (especially alcoholic cirrhosis), celiac disease, HIV, inflammatory bowel disease, and others. In addition, an identical renal disease may occur as part of the systemic vasculitis seen in Henoch-Schönlein purpura (see Plate 4-61).

The frequency of IgAN in a renal biopsy series ranges from 5% to 10% in the United States to 35% in Asian countries. IgAN may occur at any age but is usually diagnosed in young adults, with a male : female ratio of at least 2 : 1. The clinical manifestations are diverse and can include asymptomatic hematuria and proteinuria, gross hematuria, nephrotic syndrome, and acute kidney injury. In up to one in three patients, IgAN will progress to end-stage renal disease.

PATHOGENESIS

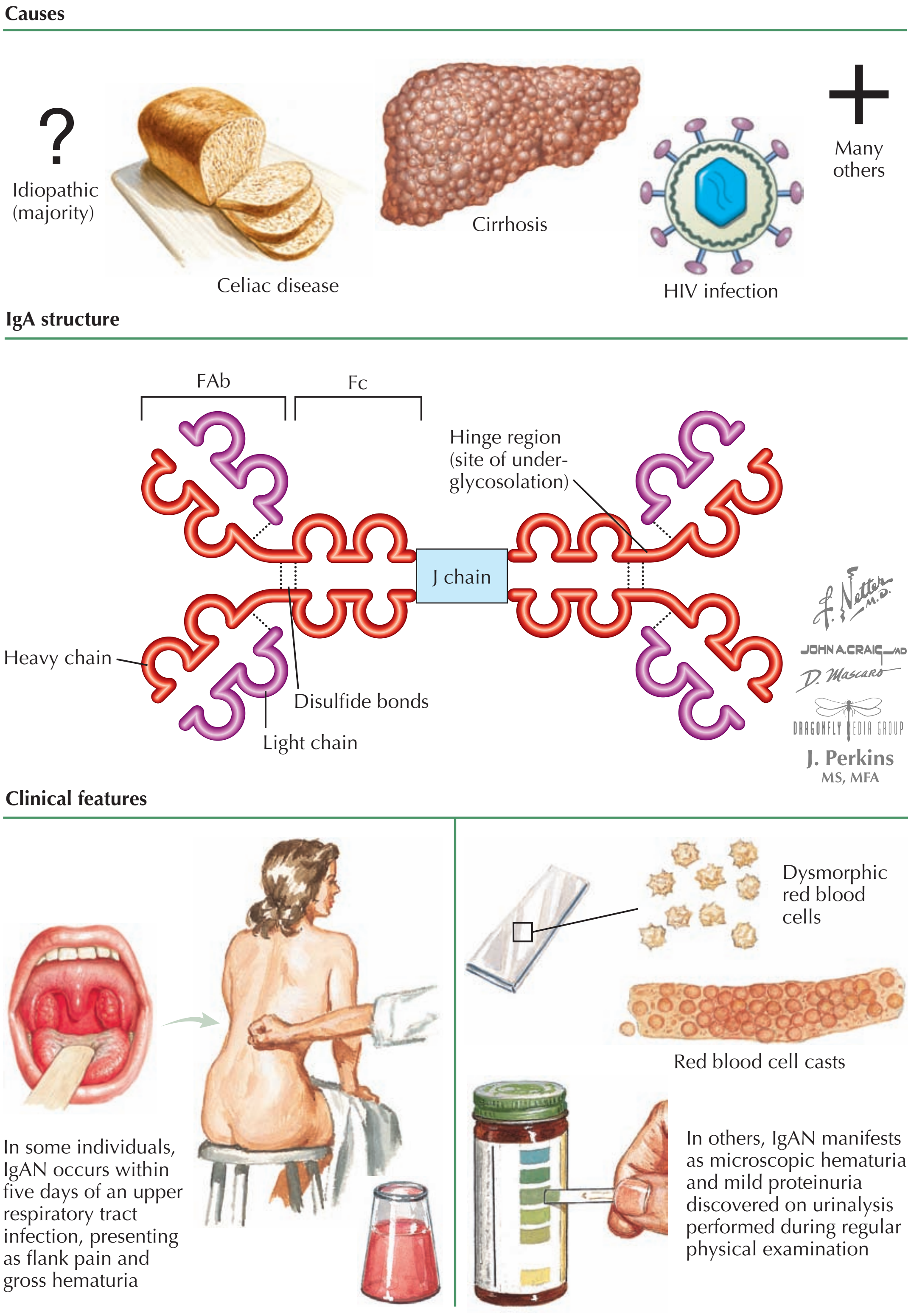
In IgAN, glomerular injury occurs when polymeric IgA1 molecules (i.e., two or more IgA1 antibodies joined by a J chain protein) deposit in the mesangium, resulting in a variable degree of glomerular hypercellularity and sclerosis.

In some patients, primary IgAN manifests as episodes of gross hematuria within 1 or 2 days of a mucosal infection. Thus it was once believed that this condition resulted from overstimulation of the mucosal immune system, which is the main site of IgA synthesis in normal individuals. Subsequent investigation, however, revealed that mucosal plasma cells actually have a decreased level of IgA production in the setting of IgAN. Instead, there is an increased number of active IgA-specific plasma cells in the systemic circulation and bone marrow. Therefore, although mucosal infections may precipitate abnormal IgA production, the polymeric IgA1 deposits derive from an abnormal systemic immune response. This process may reflect a defect in T-cell control of IgA production.

A mere increase in the production of IgA, however, is still inadequate to explain disease formation. For example, patients with myeloma or AIDS often have a significant increase in IgA levels without concomitant IgAN. Instead, it appears that the IgA molecules responsible for renal disease possess unique features that promote their accumulation within mesangial cells. In particular, there appears to be a reduced degree of glycosylation at the hinge region O-glycans, which may reflect reduced function of the enzyme β-1,3-galatosyltransferase in IgA-producing B cells. Recent studies suggest that defective IgA1 glycosylation may be an inherited risk factor.

These structural changes in the IgA molecule appear to promote mesangial deposition through multiple mechanisms, although the details are still unclear. First, the fact that the IgA molecules are in polymeric form may promote some nonspecific, size-based trapping. Second, the altered glycosylation appears to increase the affinity for mesangial extracellular matrix components, such as type IV collagen. Third, it appears that specific mesangial receptors normally bind to and clear IgA from the circulation, and that the structural changes in the IgA molecule may interfere with this process and lead to IgA accumulation. Finally, the modified IgA molecules also undergo slower systemic clearance, further promoting their accumulation.

CAUSES AND CLINICAL FEATURES OF IGA NEPHROPATHY


Causes
?
Idiopathic (majority)
Celiac disease
Cirrhosis
HIV infection
+
Many others
IgA structure
FAb
Fc
Hinge region (site of under-glycosolation)
J chain
Heavy chain
Disulfide bonds
Light chain
J. Perkins MS, MFA
Clinical features
In some individuals, IgAN occurs within five days of an upper respiratory tract infection, presenting as flank pain and gross hematuria
Dysmorphic red blood cells
Red blood cell casts
In others, IgAN manifests as microscopic hematuria and mild proteinuria discovered on urinalysis performed during regular physical examination

Once IgA binds to the mesangium, it may stimulate mesangial cell proliferation and trigger mesangial cell release of proinflammatory mediators, such as interleukin 6 and TNF-α, as well as profibrogenic mediators, such as PDGF-β and TGF-β. In addition, IgA appears to activate complement via the alternate pathway and the mannose-binding lectin (MBL) pathway. In normal circumstances, MBL activates complement when its carbohydrate recognition domain (CRD) binds to mannose residues on pathogen surfaces. In IgAN, it is possible that the CRD recognizes the abnormally glycosylated region of the IgA molecule itself. Finally, IgG may target regions of the IgA molecule and promote further inflammation.

Not all IgA that binds to the mesangium, however, is capable of generating disease. In fact, in some series up to 5% to 15% of otherwise healthy individuals are found to have glomerular IgA deposition. The specific changes in IgA that allow it to provoke inflammation after mesangial deposition, as well as the genetic features that underpin these changes, have not been identified.

IGA NEPHROPATHY *(Continued)*

Secondary IgAN may reflect either overproduction or reduced clearance of IgA. The role of abnormal glycosylation has not been adequately studied. The most common cause of secondary IgAN is chronic liver disease, which causes reduced IgA clearance. Other conditions, such as celiac disease and HIV infection, may act by increasing the levels of circulating IgA antibodies. Even in these settings, a majority of the patients found to have glomerular IgA deposits have no clinical signs of IgAN, underscoring that IgA-mesangial interactions are important for triggering pathologic changes.

PRESENTATION AND DIAGNOSIS

The clinical presentation of primary IgAN is variable. In about half of patients, especially those under 40 years of age, the disease presents as episodes of gross isolated hematuria and flank pain that occur within a few days of an upper respiratory tract infection (either bacterial or viral). These episodes are sometimes termed "synpharyngitic nephritis." The latency period is shorter than in poststreptococcal glomerulonephritis (see Plate 4-19), which tends to occur about 10 days after infection.

In about 40% of patients, and more commonly in adults, IgAN presents as microscopic hematuria and mild proteinuria (less than 2 g/day), which is detected on routine urinalysis. In 10% of patients, the proteinuria is severe enough to cause nephrotic syndrome. About 25% of patients have hypertension at the time of diagnosis, and another 25% develop hypertension over time. The age-related differences in clinical features are consistent with the existence of multiple different underlying pathogenetic mechanisms in IgAN.

In a majority of cases, serum creatinine and other markers of renal function are normal. In 5% to 10% of cases, however, acute kidney injury (AKI) occurs, reflecting either tubular obstruction by erythrocytes or fulminant disease, such as rapidly progressive glomerulonephritis (see Plate 4-25). AKI is more common in the elderly, possibly reflecting the higher incidence of coexistent chronic kidney disease in this population. In most cases, however, the pathologic features of IgAN are relatively mild, and thus renal insufficiency is not a typical presenting clinical feature.

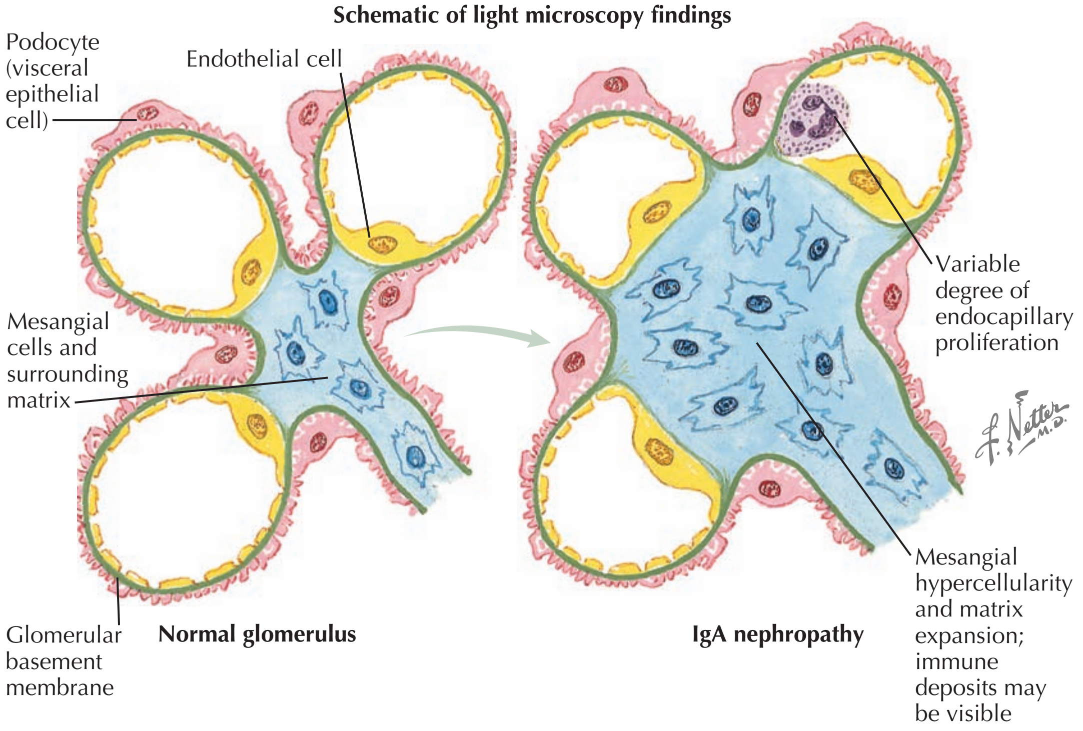
Urine microscopy typically shows dysmorphic RBCs and/or RBC casts, consistent with their glomerular origin. Serum IgA levels may be elevated in up to 50% of patients. Because complement activation is mild, serum levels of both complement C3 and C4 are normal, unlike in postinfectious glomerulonephritis or membranoproliferative glomerulonephritis.

In the absence of extrarenal symptoms suggestive of a systemic process, the differential diagnosis of glomerular hematuria with proteinuria is very broad. For cases with isolated glomerular hematuria (i.e., without proteinuria), however, the other major possibilities are thin basement membrane nephropathy and hereditary nephritis (see Plate 4-26). The likelihood of these inherited disorders can usually be determined based on a detailed family history. If the urine contains RBCs but there is no strong evidence of glomerular bleeding, such as dysmorphic cells or casts, the differential diagnosis should be expanded to include urologic diseases—such as infection, tumor, or calculi—especially if the patient is an adult.

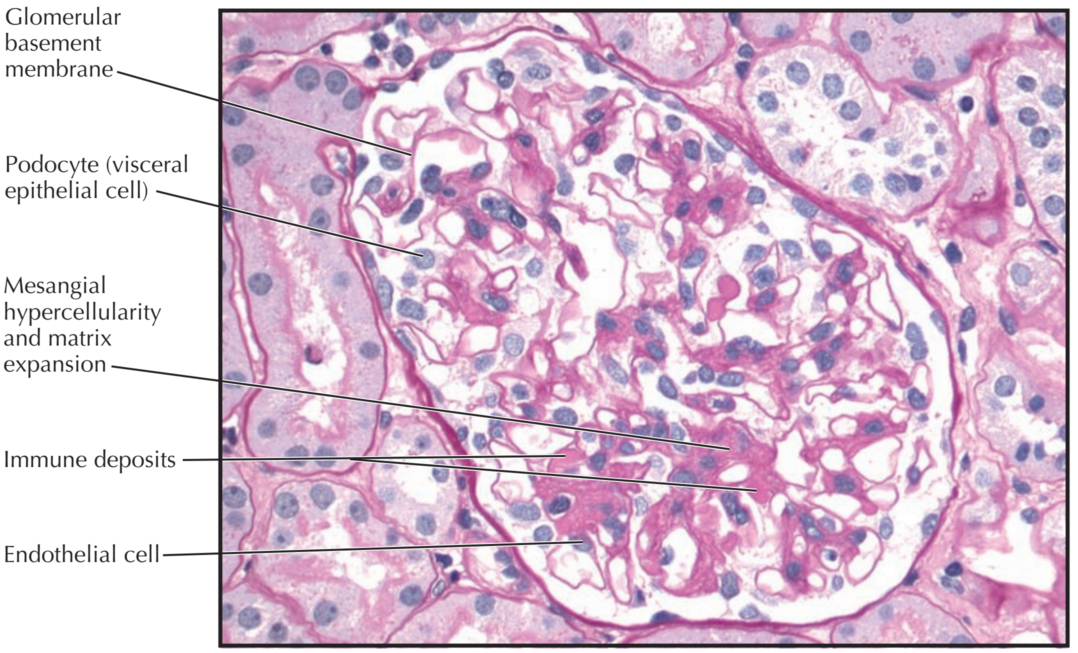
The definitive diagnostic test for IgAN is renal biopsy; however, the specific indications for this procedure vary in different countries. In the United States, biopsy is generally reserved for cases with at least mild proteinuria (>1 g/day) and/or renal insufficiency in addition to hematuria.

HISTOPATHOLOGIC FINDINGS OF IGA NEPHROPATHY

Schematic of light microscopy findings


Podocyte (visceral epithelial cell)
Endothelial cell
Mesangial cells and surrounding matrix
Glomerular basement membrane
Normal glomerulus
IgA nephropathy
Variable degree of endocapillary proliferation
Mesangial hypercellularity and matrix expansion; immune deposits may be visible
F. Netter M.D.

Light microscopy findings


Glomerular basement membrane
Podocyte (visceral epithelial cell)
Mesangial hypercellularity and matrix expansion
Immune deposits
Endothelial cell

PAS stain

Mild to moderate mesangial hypercellularity is typically seen using light microscopy. A subset of cases feature endocapillary hypercellularity, which can be segmental or global, focal or diffuse, and with or without sclerosing lesions. Proliferation and sclerosis often coexist in the same biopsy, which suggests that proliferative lesions lead to scarring and sclerosis. Extracapillary cellular crescents (see Plate 4-25) may occur if there is diffuse endocapillary hypercellularity, but these rarely involve more than 50% of glomeruli. IgA immune deposits may be seen in the mesangium and, in cases with endocapillary proliferation, the subendothelium.

The degree of tubular atrophy and interstitial fibrosis generally reflects the degree of glomerular scarring. Tubules may contain intraluminal RBCs. In cases of severe hematuria, the RBCs may cause tubular obstruction with subsequent tubular injury. In cases

IgA Nephropathy *(Continued)*

with long-standing hematuria, tubules may show hemosiderin granules. If there is hypertension, arterial vessels typically show a proportionate degree of mild to moderate medial sclerosis and intimal fibrosis. True vasculitis, however, is rare and suggests the alternative diagnosis of Henoch-Schönlein purpura.

On immunofluorescence (IF) microscopy, granular mesangial IgA deposits are seen; dominant or codominant IgA deposition is diagnostic of IgAN. A variable degree of subendothelial deposition may also be seen, which correlates with the degree of endocapillary hypercellularity. IgG and IgM deposits are present in up to 50% of IgAN biopsies, but their staining intensity should not exceed that of IgA. C3 deposits are usually present but C1q staining is typically absent.

Electron microscopy demonstrates electron dense deposits at sites corresponding to the IF staining pattern, which is typically mesangial and, less commonly, subendothelial. Endothelial tubulo-reticular inclusions should not be present because they suggest the alternate diagnosis of lupus nephritis. Podocyte foot process effacement is usually focal and confined to capillary loops that have either sclerosis or endocapillary hypercellularity (and subendothelial deposits). The finding of diffuse (>50%) foot process effacement in a majority of capillary loops, without accompanying subendothelial deposits, is seen in cases of IgAN with coexistent minimal change disease (MCD).

The pathologic findings of dominant or co-dominant IgA glomerular staining are identical to those seen in renal biopsies of patients with Henoch-Schönlein purpura (HSP, see Plate 4-61). IgAN and HSP are thus distinguished based on the presence or absence of extrarenal disease. HSP is a multisystem vasculitis affecting small vessels of the skin, gut, and kidney. Purpura occurs in all cases, whereas arthritis/arthralgias, abdominal pain, and/or renal involvement occur in a subset.

TREATMENT

No specific therapy is indicated for those with isolated hematuria. Instead, such patients should be closely monitored for the development of hypertension, proteinuria, or renal insufficiency.

In contrast, all patients with proteinuria should be started on an ACE inhibitor or ARB, regardless of blood pressure level, because of their antiproteinuric effect. High-dose fish oil supplements may also help reduce proteinuria and slow the progression of disease in patients with proteinuria >1 g/day and renal insufficiency; however, their effects have been inconsistent in clinical trials.

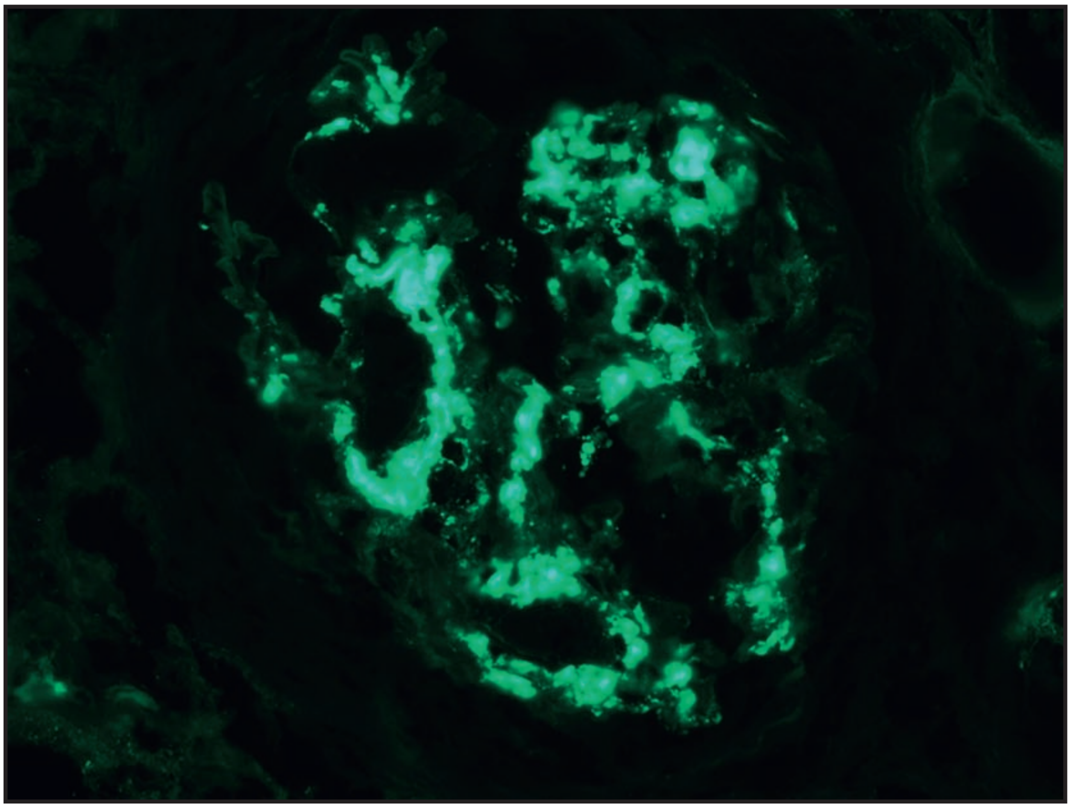
Patients with persistent proteinuria (typically >1 g/day) are typically candidates for immunosuppression with steroids. A typical 6-month regimen uses pulse methylprednisolone for 3 days during months 0, 3, and 6, with daily oral prednisone for all 6 months. For those patients with rapidly progressive glomerulonephritis and extensive crescent formation, the administration of steroids and cyclophosphamide may improve prognosis. The benefit of other agents, such as cyclosporine and mycophenolate mofetil, has not been proven.

PROGNOSIS

The rate of progression is typically slow, with about half of patients progressing to ESRD within 20 years of diagnosis.

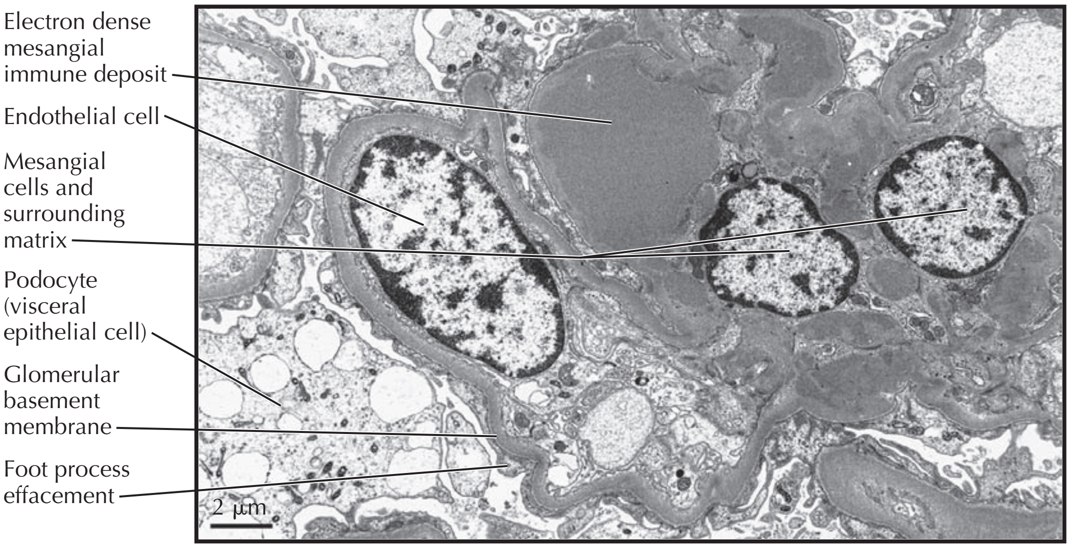
Histopathologic Findings of IgA Nephropathy (continued)

Immunofluorescence



Positive staining for IgA localized predominantly to the mesangium

Electron microscopy


Electron dense mesangial immune deposit
Endothelial cell
Mesangial cells and surrounding matrix
Podocyte (visceral epithelial cell)
Glomerular basement membrane
Foot process effacement
2 μm

The clinical features associated with worse outcomes include persistent proteinuria (>1 g/day), elevated serum creatinine concentration at diagnosis, and poorly controlled hypertension.

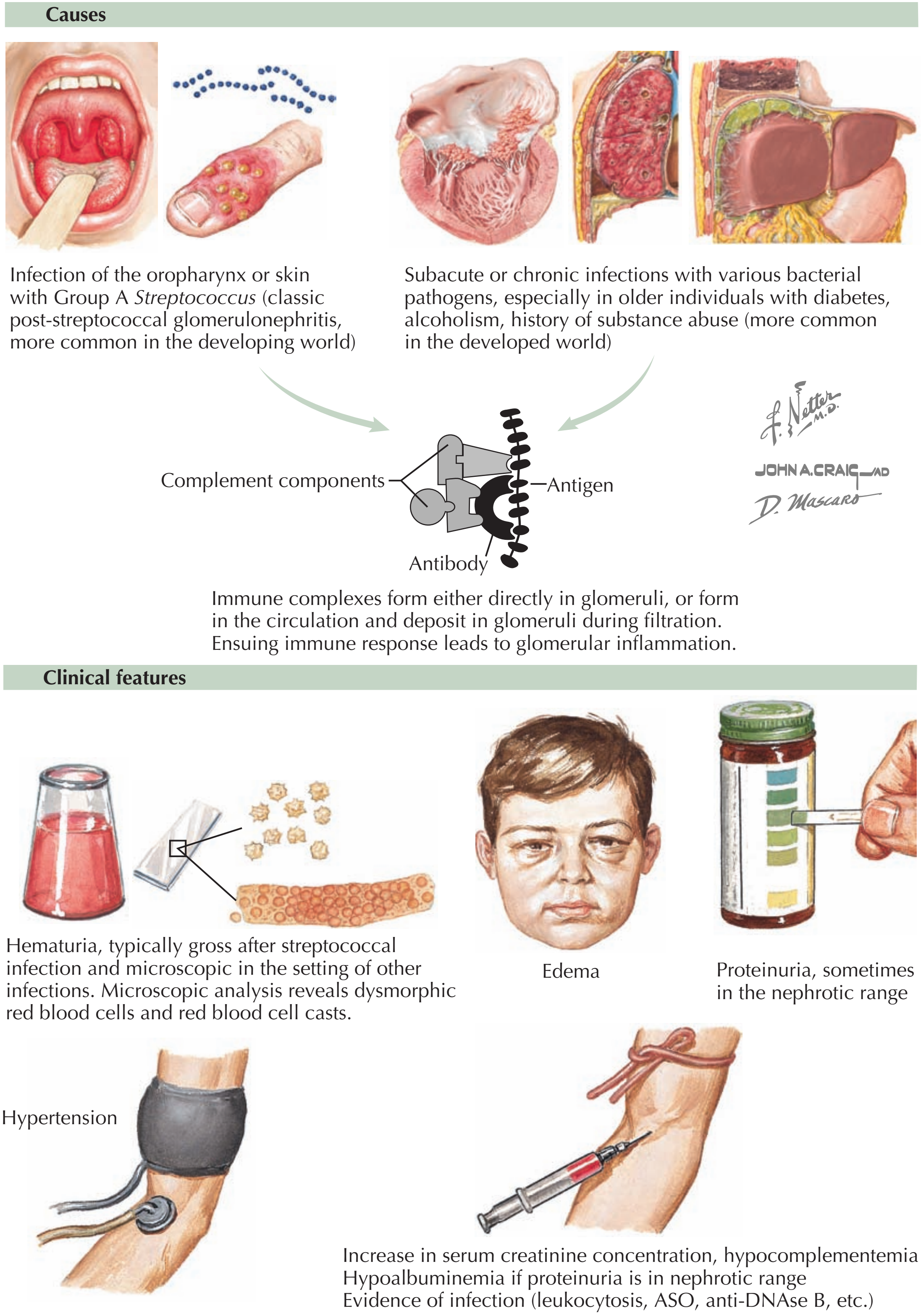
The pathologic features associated with worse outcomes include moderate to severe mesangial hypercellularity, the presence of endocapillary hypercellularity, segmental sclerosis, and tubular atrophy/interstitial fibrosis affecting more than 25% of the cortical area. Similarly, the presence of extensive cellular crescent formation portends worse outcomes.

Although IgA deposition recurs in up to 50% of renal allograft recipients, this is usually an isolated immunohistochemical finding, without significant glomerular hypercellularity or clinical signs of disease (e.g., hematuria and proteinuria). Graft loss from recurrent IgAN is rare.

Compared with primary IgAN, secondary IgAN appears to have a lower rate of progression to end-stage renal disease. In most cases, the clinical course is dominated by the underlying disease (e.g., alcoholic cirrhosis).

POSTINFECTIOUS GLOMERULONEPHRITIS

CAUSES AND CLINICAL FEATURES OF POSTINFECTIOUS GLOMERULONEPHRITIS


Causes
Infection of the oropharynx or skin with Group A *Streptococcus* (classic post-streptococcal glomerulonephritis, more common in the developing world)
Subacute or chronic infections with various bacterial pathogens, especially in older individuals with diabetes, alcoholism, history of substance abuse (more common in the developed world)
Complement components
Antigen
Antibody
Immune complexes form either directly in glomeruli, or form in the circulation and deposit in glomeruli during filtration. Ensuing immune response leads to glomerular inflammation.
Clinical features
Hematuria, typically gross after streptococcal infection and microscopic in the setting of other infections. Microscopic analysis reveals dysmorphic red blood cells and red blood cell casts.
Edema
Proteinuria, sometimes in the nephrotic range
Hypertension
Increase in serum creatinine concentration, hypocomplementemia
Hypoalbuminemia if proteinuria is in nephrotic range
Evidence of infection (leukocytosis, ASO, anti-DNAse B, etc.)

Postinfectious glomerulonephritis (PIGN) is a syndrome of glomerular injury that occurs as a result of the immune system's response to certain infections. The archetypal example is poststreptococcal glomerulonephritis (PSGN), an acute nephritis that develops following streptococcal infections of the skin or throat, and among the oldest described nephrologic diseases. Many infections can cause PIGN, but the unifying feature is immune complex deposition in the glomerulus that triggers inflammatory injury.

PATHOPHYSIOLOGY

A variety of bacteria, fungi, viruses, and parasites have been specifically associated with certain patterns of glomerular injury, including membranoproliferative glomerulonephritis (see Plate 4-22) and membranous nephropathy (see Plate 4-12).

Most clinically evident PIGN, however, results from bacterial infections. Classically, PIGN occurs in children after infection of the skin or oropharynx with specific nephritogenic strains of Group A *Streptococcus* (GAS). Although this picture remains true in the developing world, recent series from developed countries show *Staphylococcus* spp. now equaling or outnumbering *Streptococcus* spp. as the most common cause of PIGN. In addition, as many as one third to one half of cases are caused by Gram-negative organisms. Furthermore, those at risk are no longer children but rather adults over the age of 40, often with medical comorbidities such as diabetes and alcoholism. These epidemiologic shifts are most likely due to widespread availability and use of antibiotics for the treatment and prophylaxis of bacterial pharyngitis.

While the full pathogenesis of PIGN is incompletely understood, it is known to occur in only a minority of patients infected with recognized nephritogenic organisms. This observation implies that host susceptibility factors play a crucial role, in addition to specific traits of the infectious organisms themselves.

Fundamentally, nephritogenic infections present certain pathogenic antigens to the immune system, which responds by generating antibodies and forming immune complexes. These complexes may either form in the circulation and then deposit in the glomerulus during filtration, or they may form in the glomerulus in situ. Classically, immune complex deposits are found in the subepithelial space. The complexes activate complement (especially the alternative pathway) and lead to the recruitment of inflammatory cells (such as macrophages) to the glomerulus, producing immune-mediated damage.

One postulated mechanism underlying this process is molecular mimicry, in which the infectious organism presents antigens that, by coincidence, are structurally similar to normal components of the glomerular filtration barrier, such as laminin or collagen. Consequently, the immune response against the organism becomes inadvertently directed against the glomerulus as well.

Another potential mechanism for immune complex formation is that the infectious organism produces specifically nephritogenic antigens that bind to the glomerular capillary wall and activate an immune response. In the case of PSGN, two proteins produced by streptococci bear special mention: nephritis-associated streptococcal plasmin receptor (NAPlr) and streptococcal cationic proteinase exotoxin B (SpeB). NAPlr is thought to bind to glomeruli, where it captures plasmin and leads to activation of the alternative complement pathway. SpeB, with its zymogen precursor zSpeB, is an exotoxin produced by *Streptococcus pyogenes* that also binds plasmin and can activate leukocytes. One series of patients with PSGN reported the presence of glomerular deposits containing SpeB in 12 of 17 biopsies, and circulating antibodies to SpeB in all patients (53 of 53).

PRESENTATION AND DIAGNOSIS

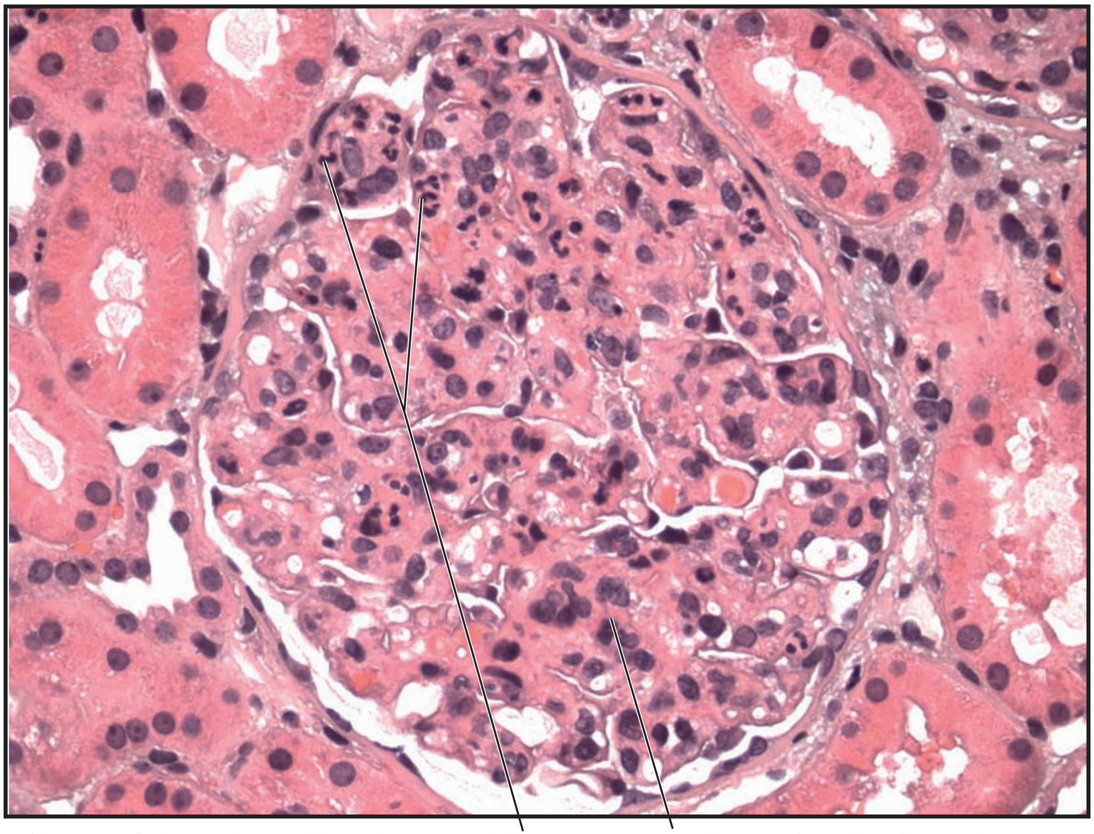
The clinical manifestations of PIGN are variable and depend on characteristics of both host and pathogen.

Poststreptococcal disease (PSGN) classically presents as a child aged 5 to 12 who develops gross hematuria 1020 days after a bout of pharyngitis or pyoderma. It typically causes an acute nephritic syndrome, with microscopic or gross hematuria, proteinuria, and hypertension. Often, facial edema and a mild decrease

POSTINFECTIOUS GLOMERULONEPHRITIS *(Continued)*

HISTOPATHOLOGIC FINDINGS OF POSTINFECTIOUS GLOMERULONEPHRITIS

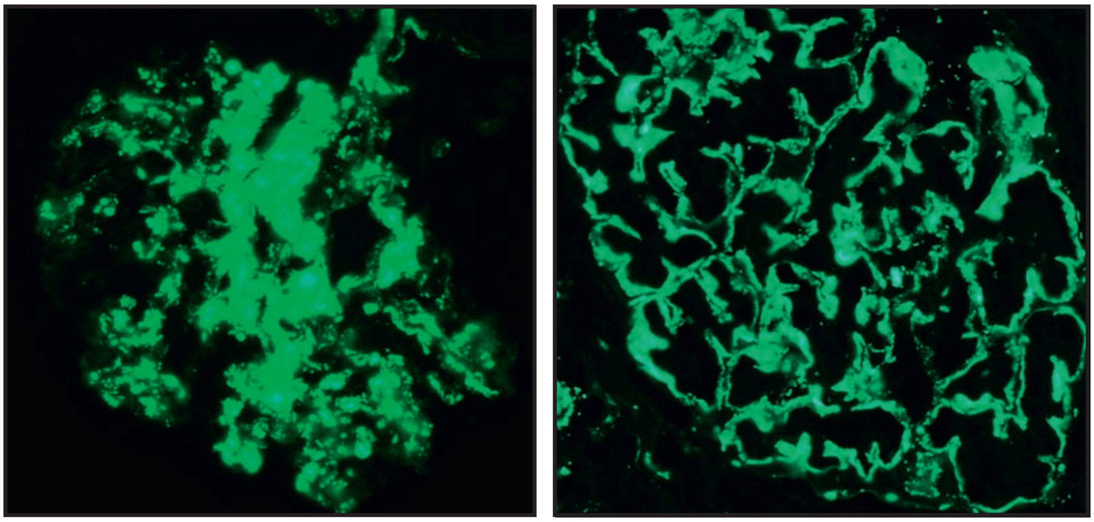
Light microscopy (H&E stain)



Infiltration of glomerular capillaries by neutrophils

Occlusion of capillary lumina by endothelial and mesangial proliferation

Immunofluorescence



Starry sky pattern (diffuse, granular staining for C3 in mesangium and capillary walls)

Garland pattern (granular staining for C3 localized to the capillary walls)

in renal function are seen as well. Occasionally the proteinuria is severe enough to cause nephrotic syndrome. In less than 1% of cases, rapidly progressive glomerulonephritis occurs, leading to severe renal failure that requires dialysis. When confronted with a child who has gross hematuria following an upper respiratory infection (URI), the crucial differential is between PSGN and IgA nephropathy (IgAN), which can have similar presentations. The key to diagnosis comes from the history and lies in the latency period between pharyngitis and hematuria; for PSGN, it usually takes 10 to 14 days for the hematuria to develop (or even 3 weeks following skin infection), whereas in IgAN hematuria occurs within 5 days of URI. Patients with IgAN may also report having similar hematuric episodes in the past.

As opposed to "classic" PSGN, PIGN in the developed world most commonly occurs in older individuals with subacute or chronic infections (acute and subacute bacterial endocarditis, pulmonary infections, visceral abscesses, infected ventriculoatrial shunts) who have significant medical comorbidities, especially those causing immune compromise (such as diabetes, malignancy, and substance abuse). These infections frequently require prolonged courses of treatment, and renal abnormalities often develop before the infection is entirely eradicated. Microscopic hematuria is present in up to 90%, with greater than 1 g/day proteinuria in roughly 4 of 5 patients, and the full nephrotic syndrome in about a quarter of patients. Unlike in PSGN, however, gross hematuria is rare.

Further laboratory testing can help narrow the diagnosis to PIGN. PIGN is one of the glomerulonephritides, for example, in which serum complement levels are low (the others being lupus nephritis, MPGN, and cryoglobulinemic GN). Hypocomplementemia is present in 60% to 70% of patients with PIGN, and closer to 90% of patients with PSGN. Typically C3 is significantly depressed, whereas C4 is only slightly depressed or normal, which suggests activation of the alternate complement pathway. Of note, a child with presumed PSGN and hypocomplementemia whose complement levels do not return to normal within 8 to 12 weeks should be evaluated for MPGN.

The specific diagnosis of PSGN is supported by serologic evidence of recent streptococcal infection. Several different antistreptococcal antibodies can be measured. The most common is the antistreptolysin O titer (ASO). Although this assay is highly sensitive for recent streptococcal pharyngitis, it will be negative following 50% of streptococcal skin infections. Anti-DNAse B antibody, in contrast, is less sensitive for pharyngeal infections but is 90% sensitive for recent streptococcal skin infections. The diagnosis of PSGN can often be made clinically without a kidney biopsy, especially in children with a typical course. Indications for biopsy might include repeated negative testing for antistreptococcal serologies, persistent renal insufficiency, persistent proteinuria, or hypocomplementemia beyond 8 to 12 weeks.

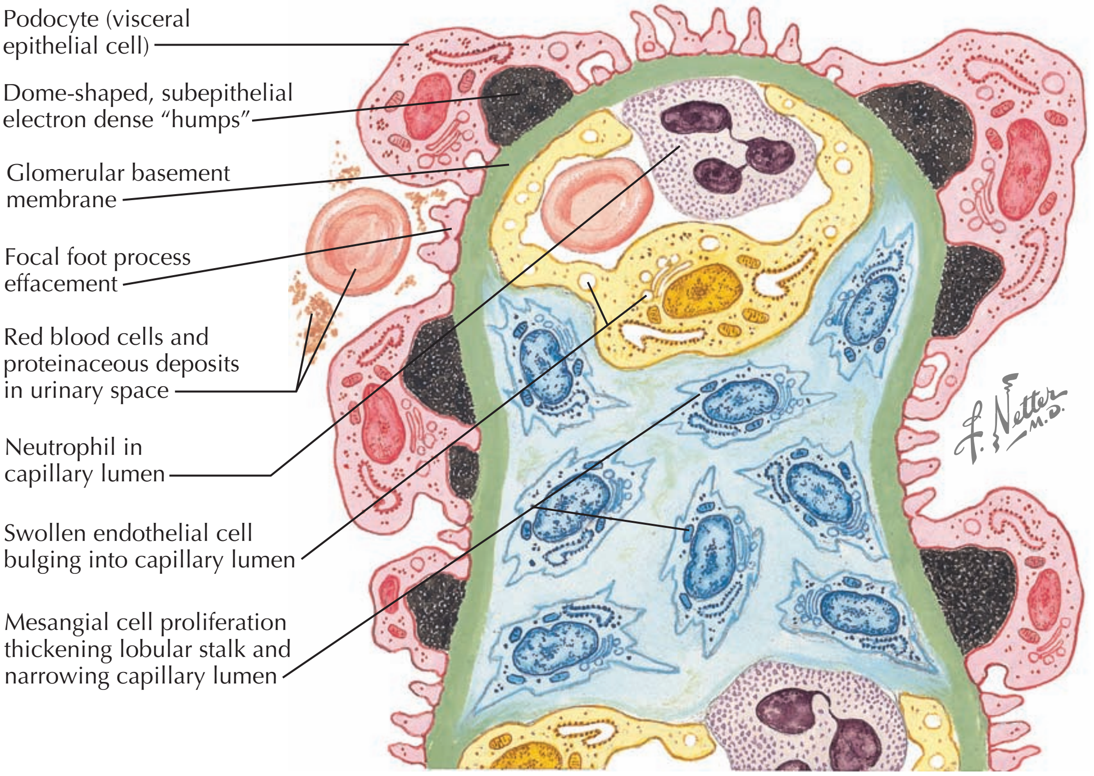
In adults with suspected PIGN, however, the picture is often clouded by the presence of medical comorbidities, comorbid renal disease, and medication or antibiotic use. Many other types of glomerular disease may be possible depending on the history, such as diabetic nephropathy, membranous nephropathy related to malignancy, or reactive amyloidosis. Older patients with atheroemboli may also have depressed complement levels and hematuria. Antibiotics used to treat active infections may cause acute interstitial nephritis or toxic tubular injury. For these reasons, a kidney biopsy becomes invaluable for elucidating the diagnosis.

Several different histologic findings may be present in PIGN, and the diagnosis can usually be made using light microscopy and immunofluorescence. On light microscopy, PIGN classically causes diffuse hypercellularity involving all of the glomeruli, with the capillary lumina obscured by endothelial proliferation, mesangial proliferation, and infiltration by monocytes and neutrophils. Silver stain may reveal characteristic postinfectious humps in the subepithelial space. These humps represent deposits of immune complexes that include complement and immunoglobulins. Immunofluorescence usually shows granular deposition of C3 and IgG, and occasionally IgM. This staining may follow the capillary wall ("garland") or it may be more diffuse ("starry sky.") Electron microscopy will show

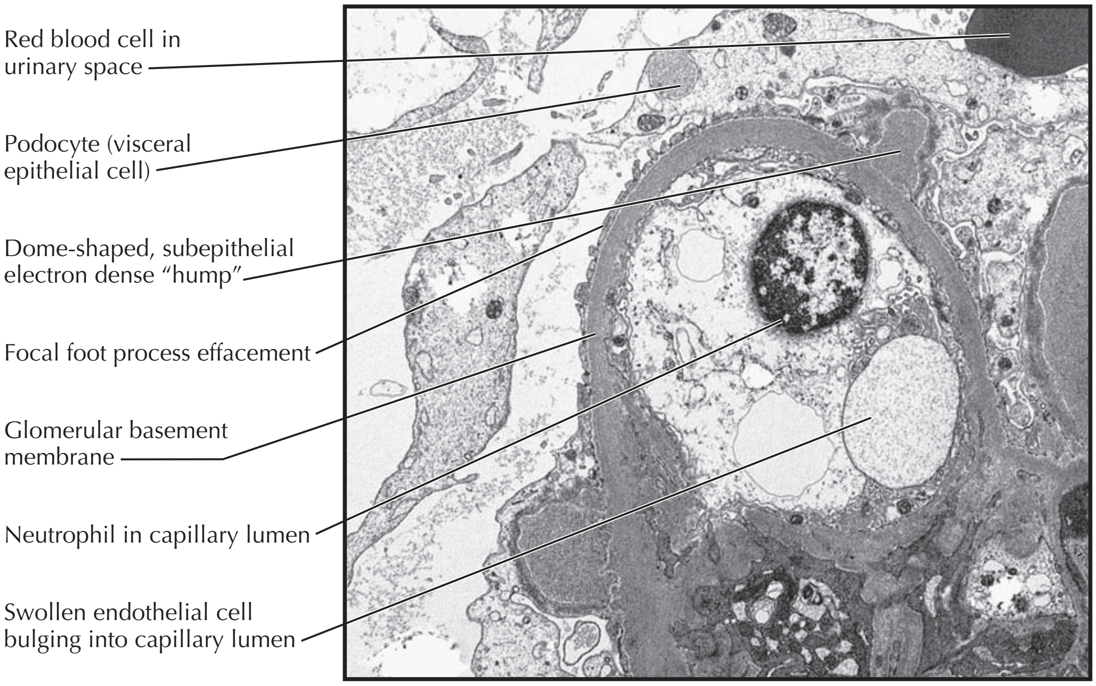
POSTINFECTIOUS GLOMERULONEPHRITIS *(Continued)*

HISTOPATHOLOGIC FINDINGS OF POSTINFECTIOUS GLOMERULONEPHRITIS (CONTINUED)

Schematic of electron microscopy findings


Podocyte (visceral epithelial cell)
Dome-shaped, subepithelial electron dense "humps"
Glomerular basement membrane
Focal foot process effacement
Red blood cells and proteinaceous deposits in urinary space
Neutrophil in capillary lumen
Swollen endothelial cell bulging into capillary lumen
Mesangial cell proliferation thickening lobular stalk and narrowing capillary lumen

Electron microscopy


Red blood cell in urinary space
Podocyte (visceral epithelial cell)
Dome-shaped, subepithelial electron dense "hump"
Focal foot process effacement
Glomerular basement membrane
Neutrophil in capillary lumen
Swollen endothelial cell bulging into capillary lumen

large dome-shaped humps in the subepithelium, and it may also show small immune complexes in the mesangium and subendothelium.

In the rare cases when acute PIGN leads to rapidly progressive glomerulonephritis, histology will show disruption of the glomerular basement membrane and the formation of cellular crescents. This presentation appears to occur more frequently with *Staphylococcus aureus* infections.

It must be noted that many people experience asymptomatic or subclinical urinary abnormalities (low-level proteinuria, pyuria, and microscopic hematuria) following trivial or self-limited bacterial or viral infections. Although the exact frequency is difficult to determine, at least one series of patients with GAS pharyngitis revealed 24% to have subclinical glomerulonephritis by urinalysis, and almost all had corresponding abnormalities (i.e., mild mesangial proliferation or hypercellularity) on kidney biopsy. An older, larger series in children found that subclinical disease was 20 times more likely than overt glomerulonephritis. These observations support the notion that a large proportion of mild and transient PIGN goes unrecognized.

TREATMENT

There is no specific treatment for PIGN other than removing the trigger for autoimmune attack. Here the term "postinfectious" can be dangerously misleading because, as previously stated, the renal disease often begins during the course of a chronic infection. To limit the inflammatory process, the infection must be identified and eradicated. A biopsy that shows PIGN with no previously suspected source should prompt a thorough investigation for occult sources of infection, including blood cultures to evaluate for subacute bacterial endocarditis, a careful dental examination, and evaluation of any indwelling foreign bodies such as ventriculoatrial shunts, vascular grafts, or pacemaker wires. Meanwhile, any person diagnosed with PSGN should be treated with a full course of antibiotics to eliminate any residual infection.

Unfortunately, PIGN may progress despite eradication of infection, especially in the setting of infection with *S. aureus* or *Brucella*. In such cases, immunosuppressive treatment is sometimes attempted. Similarly, in crescentic PIGN there has been anecdotal use of corticosteroids and or cytotoxic agents with some success. No high-quality clinical trials, however, have been performed.

A separate issue is the question of routine antibiotic treatment of pharyngitis to prevent the development of PSGN. Because the majority of pharyngitis cases are not caused by GAS, and because even GAS pharyngitis usually has a benign course, empiric antibiotics are discouraged. Several useful clinical decision algorithms to predict the likelihood of bacterial pharyngitis and guide antibiotic therapy have been proposed, such as the Centor criteria. Indeterminate scores should not be treated with antibiotics unless there is a positive rapid streptococcal antigen test or a positive throat culture. The exception is for epidemics of GAS, where close contacts to infected cases should receive prophylactic treatment with penicillin.

PROGNOSIS

The prognosis for PIGN varies according to age and comorbidities. The prognosis for children with PSGN is excellent; nephritic symptoms usually begin to improve within a week of presentation, and full recovery is the norm. Approximately 20% of children may have persistent urinary abnormalities over the long term (5 to 18 years), but impaired glomerular filtration is uncommon.

In adults, the prognosis is much worse, likely in large part due to the underlying comorbidities and chronic infections that predispose to PIGN. Only about half of patients will achieve complete remission of their renal disease. Poor prognostic indicators include age over 60 years, nephrotic-range proteinuria, "garland" immunofluorescence pattern, and crescentic glomerulonephritis. Especially poor outcomes occur in patients with underlying diabetic glomerulosclerosis, with one study reporting all affected patients having permanently impaired renal function and more than 80% reaching ESRD during a mean follow-up of 19 months.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular disease that can occur either as an idiopathic, primary phenomenon or secondary to numerous systemic conditions. It is a rare disorder, and its incidence appears to be decreasing, particularly in the developed world.

MPGN is sometimes known as "mesangiocapillary glomerulonephritis" because the major histologic features include mesangial expansion, thickening of glomerular capillaries, and interposition of mesangial matrix into the glomerular basement membrane. Alternatively, because of the lobular appearance of the glomerulus following mesangial expansion, MPGN is sometimes termed "lobular glomerulonephritis." These morphologic changes are responsible for the major symptoms of this disorder, which include hematuria and a variable degree of proteinuria.

There are three subtypes of MPGN, which are distinguished based on their electron microscopy features:

Type I MPGN—immune complex deposits seen mainly in the glomerular capillary subendothelium and mesangium.

Type II MPGN (Dense Deposit Disease)—diffuse, electron-dense, intramembranous deposits seen within the glomerular, tubular, and arteriolar basement membranes

Type III MPGN—a morphologic variant of type I MPGN with prominent subepithelial deposits.

PATHOPHYSIOLOGY

Activation of the complement system appears to be the central, unifying pathophysiologic mechanism in all MPGN subtypes. Indeed, "hypocomplemententemic glomerulonephritis" is yet another term often used to imply MPGN. The specific cause of complement activation, however, appears to differ among the subtypes.

In type I MPGN, the most common form, immune complexes deposit in the mesangium and glomerular subendothelium, then activate the classical complement pathway. These immune complexes can be either idiopathic or secondary to other disease processes, including chronic infections (chronic hepatitis C with or without detectable cryoglobulinemia, chronic hepatitis B, subacute bacterial endocarditis, infected ventriculoatrial shunt, malaria, schistosomiasis), autoimmune disease (systemic lupus erythematosus, Sjögren syndrome), and hematologic disorders (essential cryoglobulinemia, Waldenström macroglobulinemia, chronic lymphocytic leukemia).

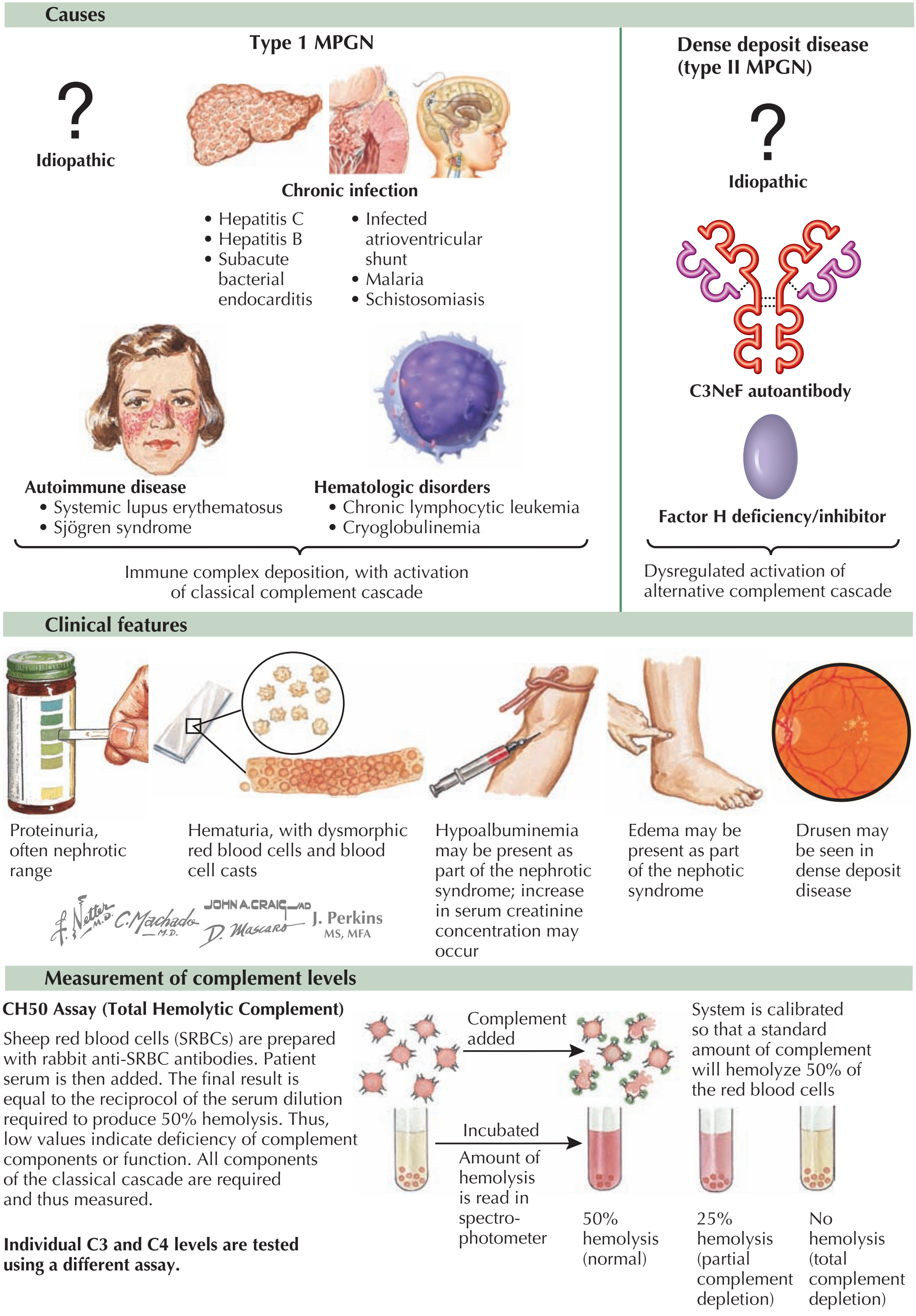
The exact proportion of idiopathic versus secondary type I MPGN is difficult to estimate; however, in recent years, it has been appreciated that HCV and cryoglobulinemia are responsible for many of the cases that had previously been considered idiopathic. Cryoglobulins are proteins that precipitate when blood is cooled below 37° C. They mostly consist of immunoglobulin and complement components, and they are found in conditions of chronic immune stimulation or lymphoproliferation, such as hepatitis C infection, HIV infection, and lymphoproliferative disorders.

In DDD, complement activation is antibody-independent and instead occurs in the setting of dysregulated activation. Moreover, complement activation follows the alternative rather than classic pathway. Complement activation occurs by two major mechanisms. At least 80% of patients produce an autoantibody known as C3 nephritic factor (C3NeF), which stabilizes C3 convertase. In a smaller fraction of patients, there is functional loss of factor H, the major inhibitor of C3 convertase, because of either genetic mutations or antifactor H antibodies. Both C3Nef and loss of factor H cause chronic overactivation of C3 convertase, with subsequent complement activation and C3 consumption.

The pathogenesis of type III MPGN appears similar to that of type I MPGN. Indeed, many consider type III MPGN to be a morphologic variant of type I, although the pathogenetic mechanisms underlying the differences seen on electron microscopy remain poorly understood.

In all MPGN types, complement activation drives injury to the glomerular capillaries and mesangium. Inflammatory cells, especially monocytes, may be recruited to various degrees and contribute to the damage. Following inflammation, reactive processes of cellular proliferation and repair cause mesangial matrix

CAUSES, FEATURES, AND ASSESSMENT OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS


Causes
Type 1 MPGN
?
Idiopathic
Chronic infection
• Hepatitis C
• Hepatitis B
• Subacute bacterial endocarditis
• Infected atrioventricular shunt
• Malaria
• Schistosomiasis
Autoimmune disease
• Systemic lupus erythematosus
• Sjögren syndrome
Hematologic disorders
• Chronic lymphocytic leukemia
• Cryoglobulinemia
Immune complex deposition, with activation of classical complement cascade
Dense deposit disease (type II MPGN)
?
Idiopathic
C3NeF autoantibody
Factor H deficiency/inhibitor
Dysregulated activation of alternative complement cascade
Clinical features
Proteinuria, often nephrotic range
Hematuria, with dysmorphic red blood cells and blood cell casts
Hypoalbuminemia may be present as part of the nephrotic syndrome; increase in serum creatinine concentration may occur
Edema may be present as part of the nephrotic syndrome
Drusen may be seen in dense deposit disease
F. Netter M.D.
C.Machado M.D.
JOHN A.CRAIG MD
D. Mascaro
J. Perkins MS, MFA
Measurement of complement levels
CH50 Assay (Total Hemolytic Complement)
Complement added
Incubated
Amount of hemolysis is read in spectrophotometer
System is calibrated so that a standard amount of complement will hemolyze 50% of the red blood cells
50% hemolysis (normal)
25% hemolysis (partial complement depletion)
No hemolysis (total complement depletion)

Sheep red blood cells (SRBCs) are prepared with rabbit anti-SRBC antibodies. Patient serum is then added. The final result is equal to the reciprocol of the serum dilution required to produce 50% hemolysis. Thus, low values indicate deficiency of complement components or function. All components of the classical cascade are required and thus measured.

Individual C3 and C4 levels are tested using a different assay.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS *(Continued)*

expansion, as well as duplication of the glomerular basement membrane. By disrupting the normal components of the filtration barrier, these inflammatory processes result in hematuria and proteinuria.

PRESENTATION AND DIAGNOSIS

The different MPGN subtypes generally present in childhood and young adulthood, and all are essentially indistinguishable with respect to their renal manifestations. The most common presentation of MPGN is the nephrotic syndrome, which is present in approximately half of patients. Even in those without overt nephrotic syndrome, a varying degree of proteinuria is almost always present. Microscopic hematuria is found in nearly 90% of cases, usually featuring dysmorphic erythrocytes but occasionally red blood cell casts as well. Up to 20% of patients may have acute glomerulonephritis.

One extrarenal manifestation particular to DDD is the development of ocular deposits known as drusen. These whitish-yellow deposits lie beneath the retinal pigment epithelium and can be seen during funduscopic examination. These lesions are also characteristic of age-related macular degeneration. The reason for drusen formation in DDD is not entirely clear; however, drusen have been found to have similar oligosaccharide composition to the electron-dense glomerular deposits, implying a possible common pathogenesis. In addition, DDD is sometimes associated with acquired partial lipodystrophy (APL), a syndrome characterized by the loss of subcutaneous fat in the upper half of the body and C3 hypocomplementemia. This phenomenon, frequently associated with C3NeF, may reflect complement-dependent lysis of adipocytes expressing high amounts of complement components, such as factor D (also known as adipsin).

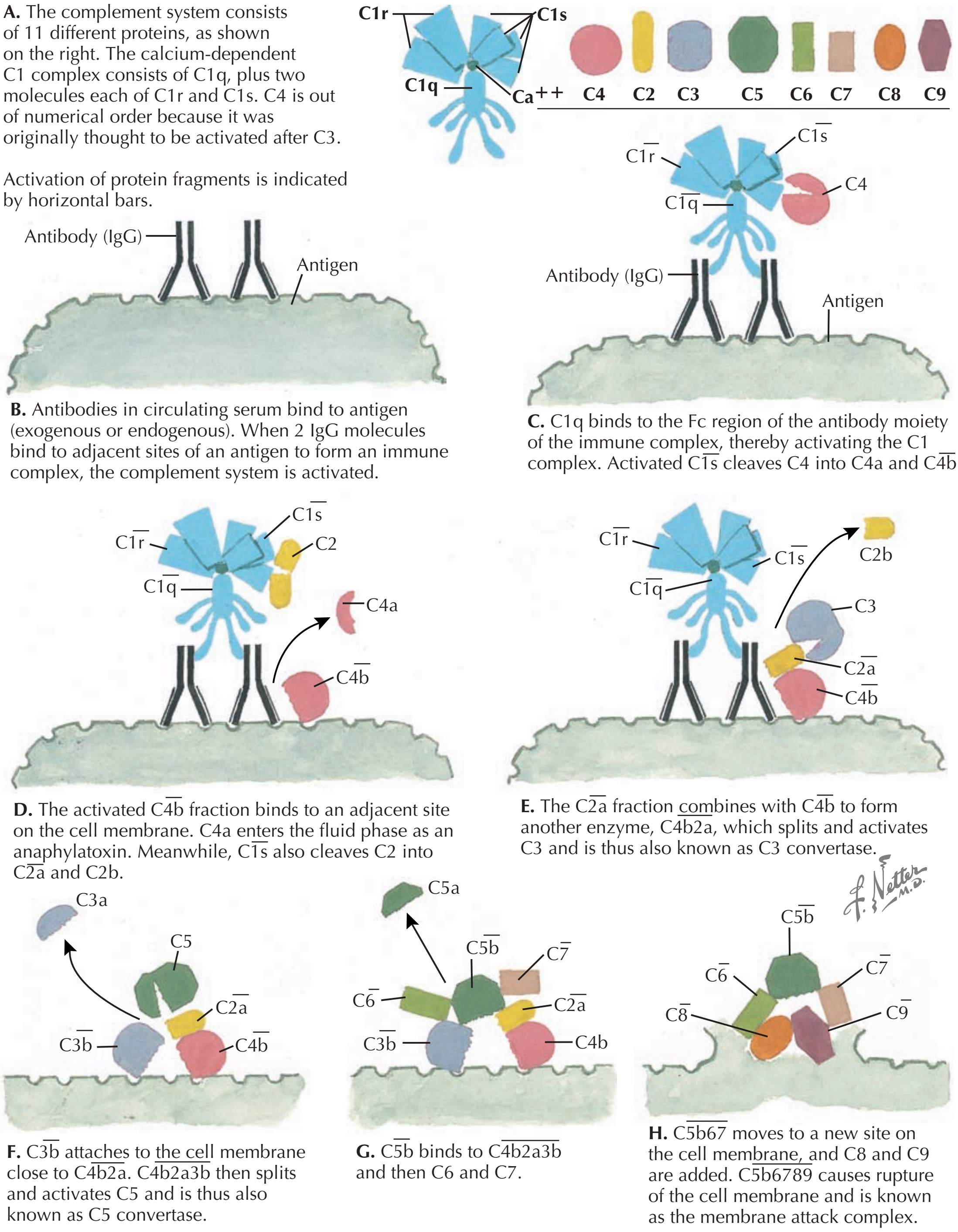
In any patient for whom MPGN is on the differential, complement levels should be assessed—specifically, C3, C4, and CH50 (total hemolytic complement, a functional assay of the complete cascade). The finding of hypocomplementemia is generally useful in the assessment of glomerulonephritis because it is present in only a few types: MPGN, cryoglobulinemic vasculitis, lupus nephritis, and postinfectious glomerulonephritis. In types I and III MPGN, where the classic pathway is activated, the typical pattern is a low or normal C3, low C4, and low CH50. In DDD, characteristically C3 is markedly decreased and CH50 is also low, whereas C4 is normal, which reflects activation of the alternative pathway. While these patterns are helpful, it must be noted that they are neither sensitive nor specific for the diagnosis of MPGN or its subtypes.

The definitive diagnosis of MPGN can only be established based on histopathologic findings. The general pattern of MPGN is usually readily recognized on light microscopy, although this modality cannot differentiate between the subtypes. Two basic features are characteristic: (1) mesangial proliferation with hypercellularity and/or matrix expansion, often leading to pronounced lobulation of the glomerulus, and (2) thickening of the capillary basement membrane. Capillary loop thickening and interposition of matrix or inflammatory cells often results in a splitting or duplication of the basement membrane, which assumes the classic double-contoured "tram track" appearance. An exudative form of MPGN can also be seen, especially in cryoglobulinemic glomerulonephritis, which is characterized by massive glomerular infiltration by inflammatory cells, particularly monocytes.

On immunofluorescence, types I and III MPGN usually show prominent granular capillary wall staining with C3, variable amounts of IgG and IgM, and sometimes C1q and C4. In contrast, in DDD the capillary wall typically stains with C3 in isolation.

The definitive distinction between MPGN subtypes can only be made with electron microscopy. In type I MPGN, immune deposits are seen in the subendothelium, whereas in type III they are also seen in the subepithelium. In DDD, pathognomonic electron-dense, intramembranous deposits are seen in the glomerular basement membrane. In many cases, these deposits are also present in the basement membranes of the tubules and arterioles. While the exact composition of the deposits has not been determined, they appear to contain glycoproteins similar to normal glomerular basement membrane, and they do not appear to contain antigenic material, immunoglobulins,

CLASSICAL PATHWAY OF COMPLEMENT ACTIVATION



A. The complement system consists of 11 different proteins, as shown on the right. The calcium-dependent C1 complex consists of C1q, plus two molecules each of C1r and C1s. C4 is out of numerical order because it was originally thought to be activated after C3.

Activation of protein fragments is indicated by horizontal bars.

B. Antibodies in circulating serum bind to antigen (exogenous or endogenous). When 2 IgG molecules bind to adjacent sites of an antigen to form an immune complex, the complement system is activated.

C. C1q binds to the Fc region of the antibody moiety of the immune complex, thereby activating the C1 complex. Activated C$\overline{1s}$ cleaves C4 into C4a and C$\overline{4b}$.

D. The activated C$\overline{4b}$ fraction binds to an adjacent site on the cell membrane. C4a enters the fluid phase as an anaphylatoxin. Meanwhile, C$\overline{1s}$ also cleaves C2 into C$\overline{2a}$ and C2b.

E. The C$\overline{2a}$ fraction combines with C$\overline{4b}$ to form another enzyme, C4b2a, which splits and activates C3 and is thus also known as C3 convertase.

F. C$\overline{3b}$ attaches to the cell membrane close to C$\overline{4b2a}$. C$\overline{4b2a3b}$ then splits and activates C5 and is thus also known as C5 convertase.

G. C$\overline{5b}$ binds to C$\overline{4b2a3b}$ and then C6 and C7.

H. C$\overline{5b67}$ moves to a new site on the cell membrane, and C8 and C9 are added. C$\overline{5b6789}$ causes rupture of the cell membrane and is known as the membrane attack complex.

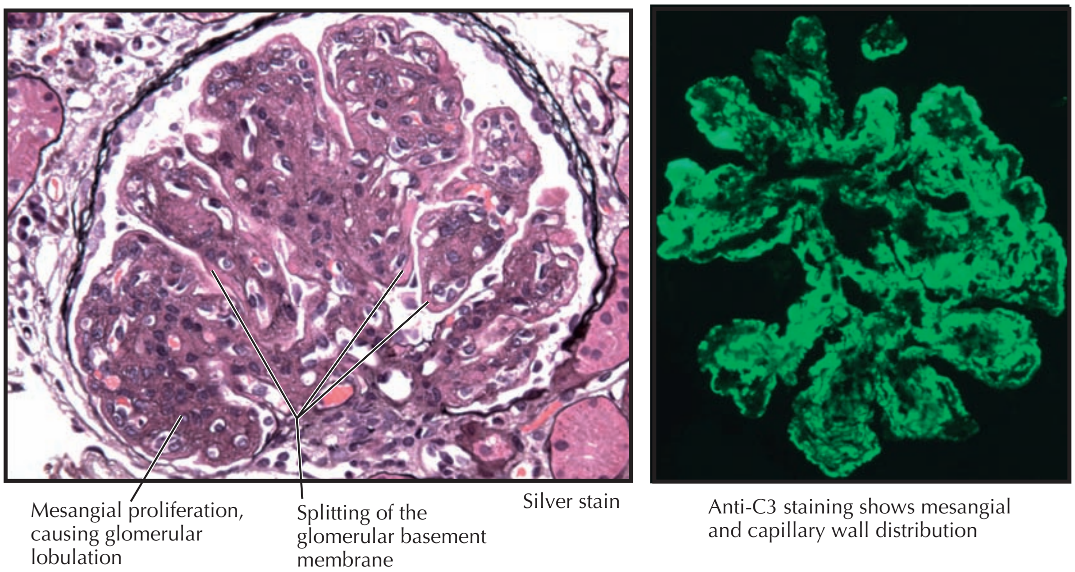
Alternative Pathway of Complement Activation: Spontaneous hydrolysis of C3 yields C$\overline{3b}$, which is stabilized on pathogen cell surfaces and binds to factors B and D. Factor D converts factor B into Ba and Bb. The C$\overline{3b}$B$\overline{b}$ complex is stabilized by properdin and then further cleaves C3 molecules, creating C$\overline{3b}$B$\overline{b}$C$\overline{3b}$, which acts as a C5 convertase. The rest of the cascade then progresses as described above.

*Note that some sources switch the names of the C2 fragments, such that C$\overline{2b}$ contributes to the C3 convertase.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS *(Continued)*

HISTOPATHOLOGIC FINDINGS OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

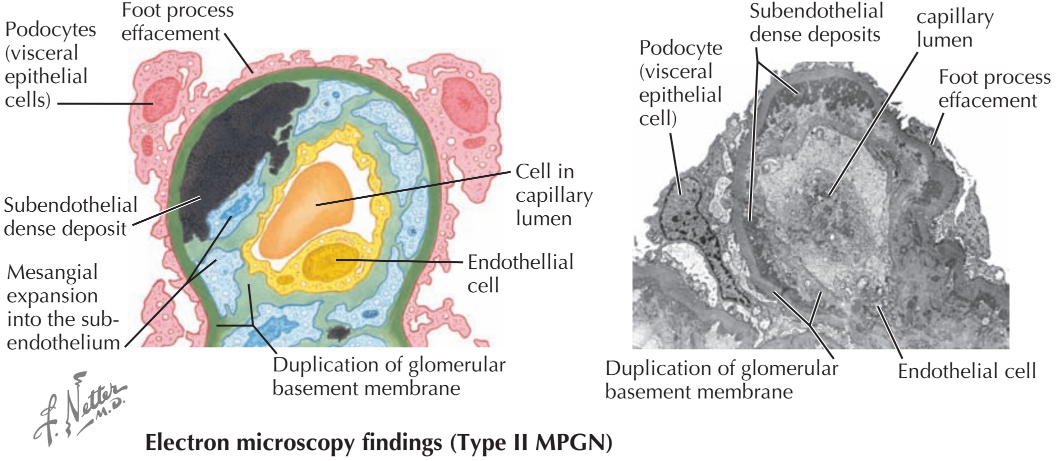
Light microscopy (Type I MPGN) **Immunofluorescence**


Mesangial proliferation, causing glomerular lobulation
Splitting of the glomerular basement membrane

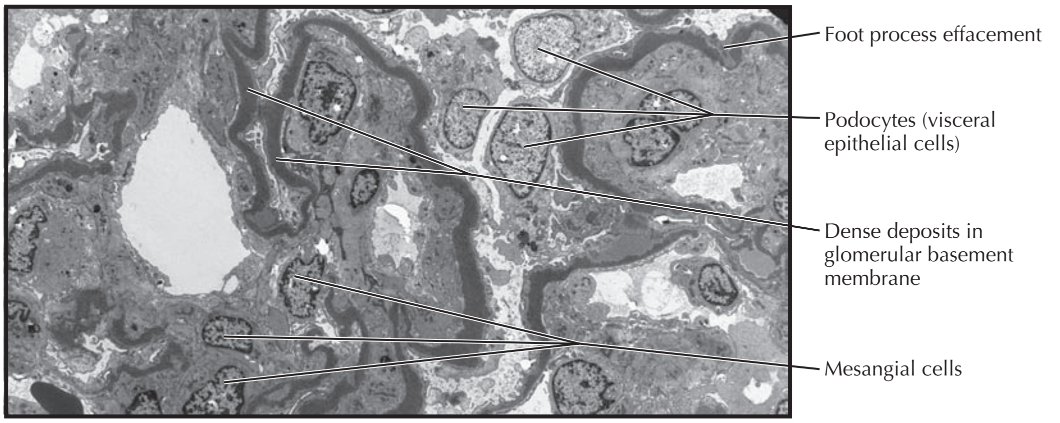
Silver stain

Anti-C3 staining shows mesangial and capillary wall distribution

Electron microscopy findings (Type I MPGN)


Podocytes (visceral epithelial cells)
Foot process effacement
Subendothelial dense deposit
Mesangial expansion into the sub-endothelium
Cell in capillary lumen
Endothellial cell
Duplication of glomerular basement membrane
Podocyte (visceral epithelial cell)
Subendothelial dense deposits
Cell in capillary lumen
Foot process effacement
Duplication of glomerular basement membrane
Endothelial cell
F. Netter M.D.

Electron microscopy findings (Type II MPGN)


Foot process effacement
Podocytes (visceral epithelial cells)
Dense deposits in glomerular basement membrane
Mesangial cells

or complement. In all subtypes, podocyte foot processes appear diffusely effaced.

If type I MPGN is diagnosed, the clinician must undertake a careful evaluation to rule out potentially causative systemic disease. This is particularly important because some of those diseases, such as parasitic infections, may be otherwise subclinical but amenable to treatment. All patients should be tested for hepatitis C and B, as well as for cryoglobulins. A negative HCV-antibody test in the presence of cryoglobulins should be interpreted with caution because the antibodies to virus may complex with the cryoglobulins and become undetectable by standard assays. If HCV is ruled out, tests for other chronic infections, autoimmune disease, or dysproteinemias should follow as appropriate. Any patient with a ventriculoatrial shunt should be considered infected until proven otherwise. Idiopathic type I MPGN should remain a diagnosis of exclusion.

If DDD is diagnosed, an assay for C3NeF should be sent and a screen for factor H mutations and activity should be performed. While none of these tests are diagnostic, they are crucial for planning therapy.

TREATMENT

Types I/III MPGN. If an underlying cause has been identified, it should be the primary focus of initial management. Eradication of chronic infection, in particular, may lead to complete resolution of the renal lesion. In HCV-associated MPGN, antiviral treatment that results in successful suppression of viral load has been shown to correlate with stabilization or regression of the renal manifestations and improvement of proteinuria. For severe disease, antiviral treatment is often accompanied by therapies aimed at reduction of circulating immune complexes, including plasmapheresis, corticosteroids, cytotoxic drugs, and rituximab.

In idiopathic disease, patients with subnephrotic proteinuria and lack of progressive renal dysfunction may be managed using conservative measures alone. These include blood pressure control and renin-angiotensin blockade to limit proteinuria. If present, hyperlipidemia should also be managed. Patients with progressive disease, in contrast, should have a trial of immunosuppression. In children, at least one reasonably large randomized controlled trial demonstrated that a course of prednisone preserved renal function better than placebo. This benefit, however, was offset by significant corticosteroid toxicity. The studies on corticosteroids in adults have been less encouraging, and it is essential that HCV be ruled out before this therapy is attempted. Various combinations of cytotoxic and immunosuppressant drugs have been used with some success, but none has been rigorously evaluated. Antiplatelet and antithrombotic agents have also been used—specifically warfarin, aspirin, and dipyridamole—with some short-term success reported in small trials. This treatment strategy is based on the postulated contribution of platelet activation to the inflammatory process in MPGN.

DDD. The treatment strategy depends on the identified cause. If C3NeF is identified, strategies to remove it include plasmapheresis, IVIg, and B-cell suppression, but success has been limited. For those few patients with identified factor H mutations, plasma exchange to replace the deficient complement factor can stabilize renal function and prevent progression to ESRD. The role of complement inhibitors (e.g., eculizumab) is under investigation.

PROGNOSIS

Outcomes in idiopathic disease are poor. More than 60% of patients with type I MPGN will progress to ESRD within 10 years of diagnosis. For DDD, the picture is even more grim, with ESRD usually occurring within 4 years of diagnosis. In all MPGN types, signs that portend a poorer prognosis include nephrotic syndrome, reduced GFR, and advanced tubulointerstitial disease. Complement levels do not correlate well with prognosis.

For patients who reach ESRD, renal transplant may be performed, but recurrence in the allograft is common unless the underlying cause has been addressed. MPGN type I has been documented to recur in 30% to 77% of allografts, leading to graft loss in 17% to 50% of cases. For DDD the prognosis is even worse, with virtually all transplanted patients experiencing recurrence and at least half eventually losing the graft as a result.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Causes

Immune complex glomerulonephritis

- *Accounts for 25% of cases*
- Post-infectious/streptococcal glomerulonephritis
- Lupus nephritis
- IgA nephropathy
- Henoch-Schönlein purpura
- Membranoproliferative glomerulonephritis

Pauci-immune (vasculitic) glomerulonephritis

- *Accounts for 60% of cases*
- Isolated renal disease
- Wegener granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome

Anti-GBM disease

- *Accounts for 15% of cases*
- Isolated renal disease
- Goodpasture syndrome

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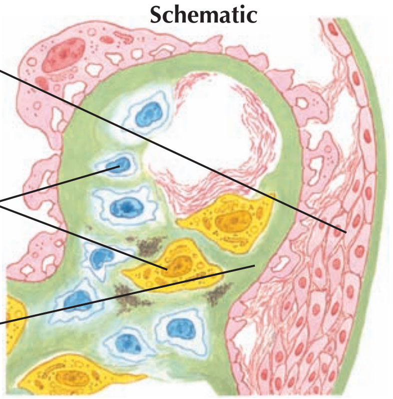
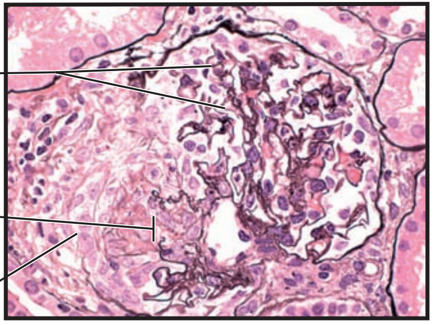
D. Mascaro

Histopathologic findings

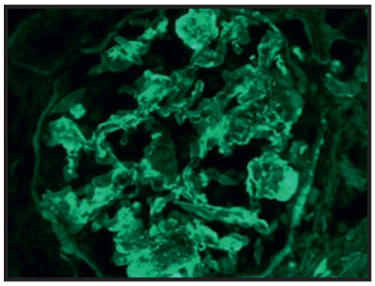
Schematic


Cellular crescent
Endocapillary proliferation, usually severe, in immune complex disease
Glomerular basement membrane (rupture not shown)

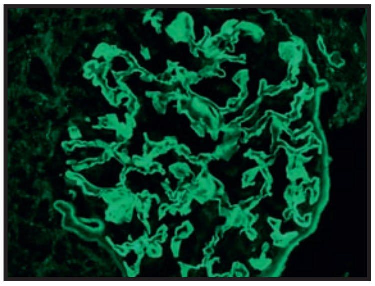
Light microscopy: Silver stain


Glomerular basement membrane
Rupture of glomerular basement membrane
Cellular crescent

Immunofluorescence



Granular staining for IgG, consistent with immune complex disease



Linear staining for IgG, consistent with anti-GBM disease

Rapidly progressive glomerulonephritis (RPGN) is a severe form of glomerulonephritis (GN) in which there is rapid loss of renal function over the course of weeks to months. Other findings are also typical of the nephritic syndrome (see Plate 4-14), including hematuria with dysmorphic red blood cells and red blood cell casts, proteinuria, oliguria, and hypertension.

RPGN is not a singular process with a unique pathophysiology; rather, it is a pattern of severe glomerular inflammation that may occur secondary to any kind of glomerulonephritis. In all cases, RPGN invariably features the histologic finding of cellular crescents. These occur when the glomerular inflammation is severe enough to cause compromise of the basement membrane, with resultant rupture of the glomerular capillary walls and leakage of inflammatory cells into Bowman's space. The crescent-shaped cellular aggregates that form along the parietal lining of Bowman's capsule consist of extravasated leukocytes, epithelial cells, and eventually myofibroblasts. The presence of crescents is the cardinal pathologic finding of RPGN, which is thus often called crescentic GN.

RPGN can occur secondary to immune complex GN, pauci-immune GN, and antiglomerular basement membrane (anti-GBM) disease (see Plate 4-14 for more details on each). These diagnostic categories are distinguished based on immunofluorescence findings.

IMMUNE COMPLEX DISEASE

Immune complex (IC) GN encompasses a large group of diseases that, in a small number of cases, are severe enough to cause RPGN. Because ICGN is so much more common than pauci-immune or anti-GBM disease, however, it accounts for approximately 25% of total RPGN cases. Any form of immune complex GN can present as RPGN, although the most common culprits are lupus nephritis (see Plate 4-49), Henoch-Schönlein purpura (see Plate 4-61), IgA nephropathy (see Plate 4-16), and postinfectious GN (see Plate 4-19).

A characteristic finding of immune complex RPGN is granular immunofluorescent staining of the mesangium or capillary wall for antibodies and complement components. When ICGN causes crescent formation, usually a smaller fraction of glomeruli (≤25%) are affected when compared with pauci-immune or anti-GBM disease (≥50%). The management of ICGN, in general, varies according to the underlying disease process. The presence of crescents, however, warrants aggressive treatment with steroids and, in many cases, cytotoxic agents.

PAUCI-IMMUNE (VASCULITIC) DISEASE

Pauci-immune (vasculitic) GN is associated with the presence of antinuclear cytoplasmic antibodies (ANCAs). It can occur as either a renal-limited phenomenon or a component of a systemic vasculitis, as with Wegener granulomatosis, microscopic polyangiitis, or Churg-Strauss syndrome (see Plate 4-25). In contrast to ICGN, pauci-immune GN almost always produces RPGN, accounting for approximately 60% of total cases. It is an especially common cause of RPGN among older adults.

A characteristic finding of pauci-immune RPGN is a relative absence of immunofluorescent staining for antibodies and complement components. Although ANCAs are typical of pauci-immune GN, they may also be present in about one quarter of those with IC RPGN and one third of those with anti-GBM RPGN.

Pauci-immune RPGN is typically very aggressive. Thus management always includes steroids and cyclophosphamide, and severe cases warrant plasmapheresis. Untreated disease is usually fatal.

ANTI-GBM DISEASE

Anti-GBM disease occurs when autoantibodies directly target the glomerular basement membrane, causing inflammation that almost always leads to RPGN. Because anti-GBM disease (either isolated or as part of Goodpasture syndrome) is rare, however, it accounts for only 15% of total RPGN cases. A characteristic finding of anti-GBM disease is smooth, linear immunofluorescent staining of the capillary wall for antibodies and complement components. Treatment consists of plasmapheresis to remove the pathogenic antibodies, along with steroids and either cyclophosphamide or azathioprine. With treatment, mortality is about 10%. Without treatment, anti-GBM disease invariably produces end-stage renal disease (ESRD). Patients who deteriorate to the point of requiring dialysis may need to continue immunomodulatory treatment to prevent pulmonary hemorrhage, but treatment usually does not result in any recovery of renal function.

EVALUATION AND TREATMENT

When a patient has a rapid decline in renal function, complement levels and serologies should be obtained (ANA, anti-DNA antibodies, ANCA, anti-GBM antibodies, cryoglobulins, hepatitis B and C), and a renal biopsy should be performed without delay. Diseases with presentations similar to RPGN but with no evidence of crescents on biopsy include thrombotic microangiopathy and atheroembolic disease. If RPGN is strongly suspected, presumptive treatment with steroids is typically initiated at the time of presentation, with further treatment dictated by the results of the renal biopsy.

HEREDITARY NEPHRITIS (ALPORT SYNDROME)/THIN BASEMENT MEMBRANE NEPHROPATHY

Hereditary nephritis (HN, also known as Alport syndrome) and thin basement membrane nephropathy (TBMN) are both inherited disorders that feature structural defects in type IV collagen, an integral component of the glomerular basement membrane. Both conditions present in childhood with persistent microscopic hematuria.

HN is rare, affecting 1 in 50,000 individuals, and often progresses to end stage renal disease (ESRD). TBMN, in contrast, affects 1 in 20 to 100 individuals and typically does not have a progressive course.

PATHOPHYSIOLOGY

Hereditary Nephritis. In the glomerular basement membrane (GBM), the α-3, α-4, and α-5 chains of type IV collagen join to form a triple helix. Normal structure and function of the GBM requires that each chain in the collagen molecule possess a normal structure. HN can be caused by mutations in the genes encoding any of these chains, which prevents them from being effectively incorporated into a helical structure.

The genes encoding the α-3 and α-4 chains (*COL4A3* and *COL4A4*) are located at chromosome 2q35-37, whereas the gene encoding the α-5 chain (*COL4A5*) is located on the X-chromosome; thus mutations can be transmitted in autosomal dominant, autosomal recessive, or X-linked patterns.

About 80% of cases result from X-linked mutations in *COL4A5*. Female carriers may have variable disease manifestations, depending on the severity of the mutation and the pattern of X-chromosome inactivation.

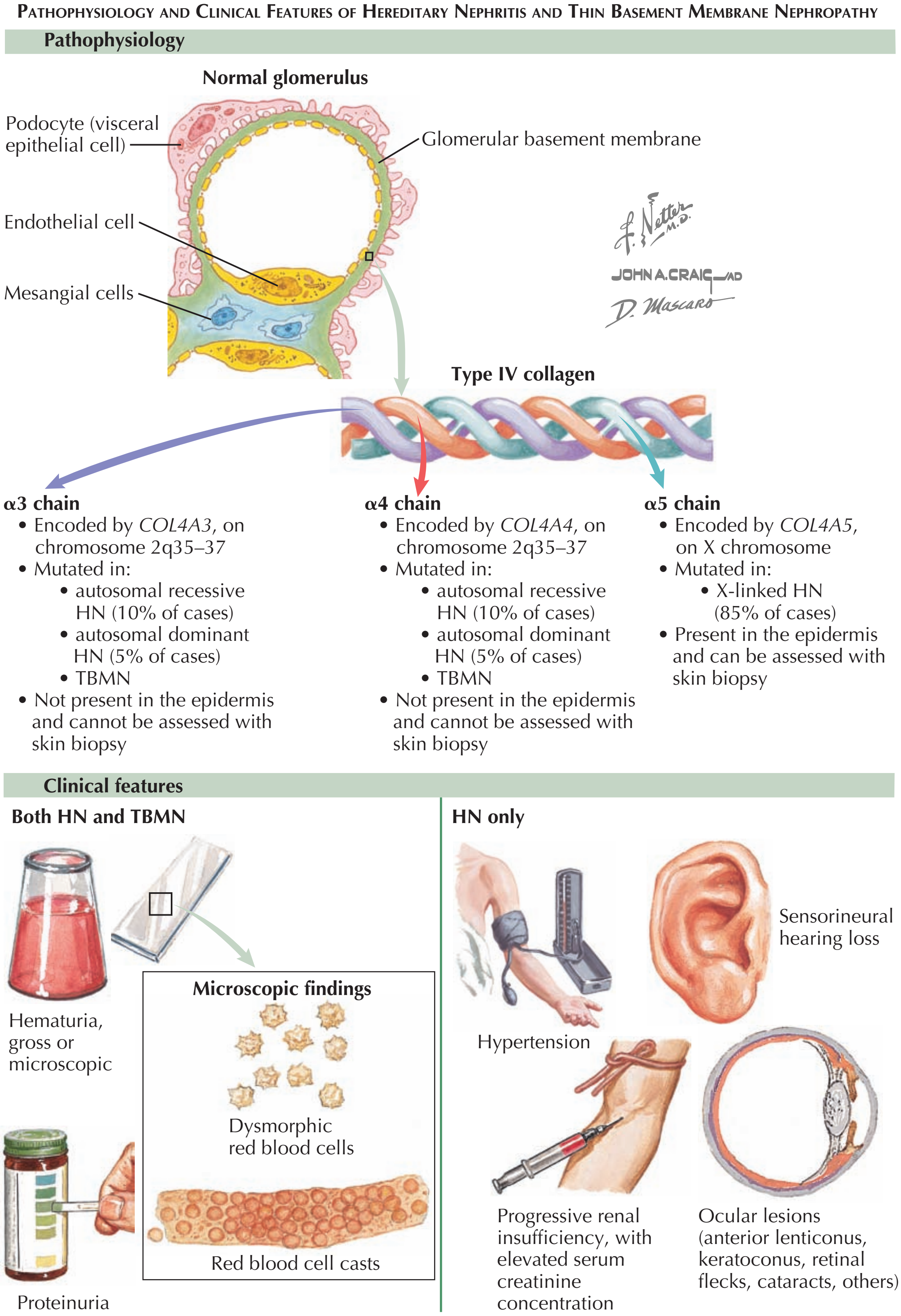
About 15% of cases reflect autosomal recessive mutations of *COL4A3* or *COL4A4*. In the remaining 5% of cases, a single mutant copy of *COL4A3* or *COL4A4* is sufficient to cause HN.

The poor integrity of the abnormal collagen IV network leads to focal ruptures and holes in the GBM, which allow red blood cells and a subnephrotic quantity of protein to enter the urine. In patients with mutations so severe that essentially no α-3/α-4/α-5 type IV collagen is produced, the GBM is composed mainly of α-1/α-1/α-2 type IV collagen, a more fragile version that usually forms the GBM during embryogenesis. GBMs composed of α-1/α-1/α-2 type IV collagen appear to be more susceptible to oxidative and physical stress.

Because type IV collagen networks are also found in the cochlea, eye, skin, lungs, testis, and smooth muscle, patients with HN may also exhibit extrarenal disease. Generally, both renal and extrarenal manifestations are more severe in patients with large deletions or frameshift mutations that severely distort the affected collagen chain.

Thin Basement Membrane Nephropathy. A substantial portion of TBMN cases reflect mutations in *COL4A3* and *COL4A4*. The inheritance is considered autosomal dominant, but in fact those with TBMN could be considered carriers of the autosomal recessive mutations responsible for HN. The fact that these patients are heterozygous for these mutations, rather than homozygous, explains their milder phenotype. While patients with HN entirely lack the ability to make a normal version of one of the α chains, patients with TBMN are able to produce some normal α-3/α-4/α-5 type IV collagen, resulting in thinner but otherwise intact GBMs. As in HN, however, these abnormal GBMs allow passage of red cells and protein into the urine.

Not all cases of TBMN can be linked to mutations in *COL4A3* and *COL4A4*. Research to better understand the spectrum of mutations that cause TBMN is ongoing. Extrarenal manifestations in TBMN are uncommon because the mutations are milder than those seen in HN and cause less severe disruptions in type IV collagen networks.



Pathophysiology and Clinical Features of Hereditary Nephritis and Thin Basement Membrane Nephropathy

Pathophysiology
Normal glomerulus
Podocyte (visceral epithelial cell)
Glomerular basement membrane
Endothelial cell
Mesangial cells
F. Netter M.D.
JOHN A.CRAIG AD
D. Mascaro
Type IV collagen

α3 chain
- Encoded by *COL4A3*, on chromosome 2q35–37
- Mutated in:
  - autosomal recessive HN (10% of cases)
  - autosomal dominant HN (5% of cases)
  - TBMN
- Not present in the epidermis and cannot be assessed with skin biopsy

α4 chain
- Encoded by *COL4A4*, on chromosome 2q35–37
- Mutated in:
  - autosomal recessive HN (10% of cases)
  - autosomal dominant HN (5% of cases)
  - TBMN
- Not present in the epidermis and cannot be assessed with skin biopsy

α5 chain
- Encoded by *COL4A5*, on X chromosome
- Mutated in:
  - X-linked HN (85% of cases)
- Present in the epidermis and can be assessed with skin biopsy

Clinical features
Both HN and TBMN
Hematuria, gross or microscopic
Microscopic findings
Dysmorphic red blood cells
Red blood cell casts
Proteinuria
HN only
Hypertension
Sensorineural hearing loss
Progressive renal insufficiency, with elevated serum creatinine concentration
Ocular lesions (anterior lenticonus, keratoconus, retinal flecks, cataracts, others)

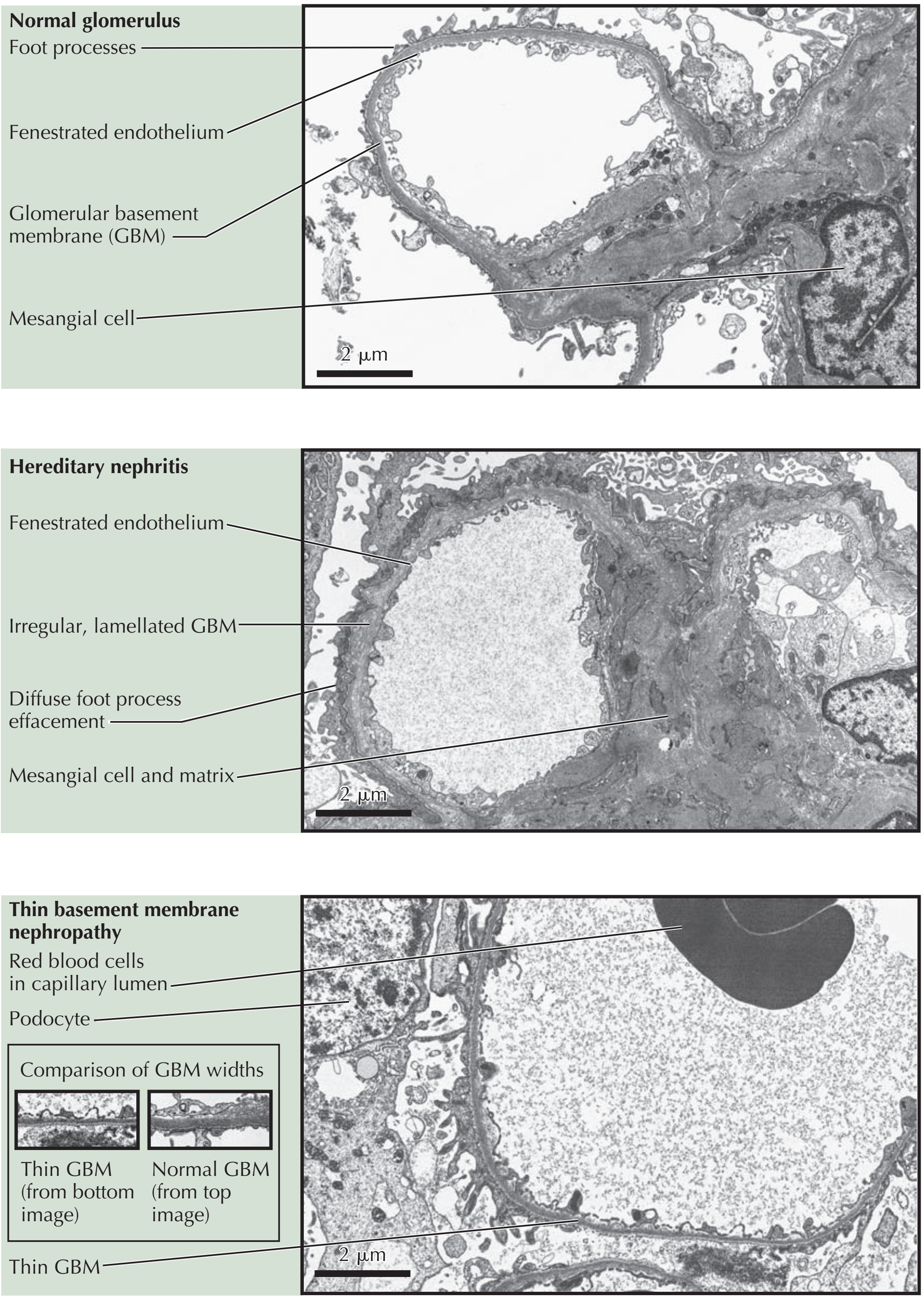
PRESENTATION

Hereditary Nephritis. Early renal manifestations of HN include persistent microscopic hematuria, usually beginning in childhood and often accompanied by intermittent episodes of gross hematuria. On microscopic

Hereditary Nephritis (Alport Syndrome)/Thin Basement Membrane Nephropathy

(Continued)

Electron Microscopy Findings of Hereditary Nephritis and Thin Basement Membrane Nephropathy


Normal glomerulus
Foot processes
Fenestrated endothelium
Glomerular basement membrane (GBM)
Mesangial cell
2 μm
Hereditary nephritis
Fenestrated endothelium
Irregular, lamellated GBM
Diffuse foot process effacement
Mesangial cell and matrix
2 μm
Thin basement membrane nephropathy
Red blood cells in capillary lumen
Podocyte
Comparison of GBM widths
Thin GBM (from bottom image)
Normal GBM (from top image)
Thin GBM
2 μm

evaluation, the RBCs often appear dysmorphic or in cast form, reflecting their glomerular origin. In the second through fourth decades of life, proteinuria, hypertension, and progressive renal insufficiency emerge. Extrarenal manifestations include sensorineural hearing loss and ocular abnormalities. Among males with X-linked disease, sensorineural hearing loss affects up to 80%, depending on how carefully screening is performed, whereas ocular abnormalities (such as anterior lenticonus, which is nearly pathognomonic of HN) affect approximately 25%.

Thin Basement Membrane Nephropathy. Patients generally have persistent microscopic hematuria. Proteinuria is infrequent in childhood but develops in a substantial portion of adults. Extrarenal manifestations are not seen. The age of diagnosis varies considerably, ranging from early childhood to late adulthood.

DIAGNOSIS

Aside from HN and TBMN, the other major cause of microscopic hematuria in children is IgA nephropathy (see Plate 4-16), which should thus be part of the differential diagnosis. A positive family history of hematuria suggests either HN or TBMN over IgA nephropathy; additional history of end-stage renal disease, deafness, or visual abnormalities suggests HN over TBMN.

If HN is suspected, the diagnosis can sometimes be established with a skin biopsy. The α-5 chain of type IV collagen is normally expressed in the epidermal basement membrane, and a lack of staining with α-5-targeted antibodies indicates a mutation is present. Since the α-5 chain is mutated in the X-linked form of the disease, this procedure will detect many affected patients. Mutations in the α-3 or α-4 chains, however, cannot be detected with a skin biopsy because these chains are not normally expressed in the epidermal basement membrane. Thus, in the setting of a negative skin biopsy, a renal biopsy is typically required.

TBMN, in contrast, is usually presumptively diagnosed based on persistent hematuria, family history, and a nonprogressive course. If a skin biopsy is performed, immunofluorescence is unremarkable because the α-5 chain is not mutated in this disease. Thus renal biopsy, though not commonly performed, is required for definitive diagnosis.

Using light microscopy, no distinctive features are seen in either HN or TBMN. Electron microscopy, in contrast, reveals diagnostic findings in both conditions. In HN, the GBM shows irregular thickening and thinning, with multiple lamellations that produce a woven texture. Diffuse foot process effacement is seen. TBMN, in contrast, shows thinning of the GBM without complex lamellations. Because the earliest alteration seen in HN is patchy GBM thinning, differentiation between these two diseases is sometimes difficult. In these settings, immunofluorescence staining for α-3, α-4, and α-5 chains may help reveal the difference. In HN, there is usually loss or severely reduced expression of all three α chains, reflecting failure to assemble normal α-3/α-4/α-5 type IV collagen chains, with α-1/α-1/α-2 chains often produced instead. TBMN, in contrast, features positive staining for α-3, α-4, and α-5 chains. Direct genetic testing may be used for prenatal diagnosis or in cases where biopsy findings are equivocal.

TREATMENT AND PROGNOSIS

HN cannot be targeted with any specific medical treatment. Control of hypertension and proteinuria through renin-angiotensin blockade may slow the progression of glomerulosclerosis and renal insufficiency. The rate of progression to ESRD varies widely and depends on the severity of the genetic mutation.

TBMN is generally a nonprogressive disease and does not result in significant scarring of the kidney. No directed therapy is needed. If a patient presumptively diagnosed with TBMN shows evidence of progressive renal disease, a renal biopsy or the other diagnostic tests mentioned previously should be considered to exclude HN and IgA nephropathy.

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis (AIN) is a major cause of intrarenal acute kidney injury (AKI) and features diffuse inflammation and edema of the tubulointerstitium. It accounts for a small fraction of AKI in general but is seen in up to 25% of patients with AKI who undergo a renal biopsy, generally after more common causes (such as prerenal state and acute tubular necrosis) have been excluded.

PATHOPHYSIOLOGY

The major known causes of AIN fall into three broad categories: drugs, infectious diseases, and autoimmune disorders. Since the implicated drugs and infectious pathogens only cause AIN in a small fraction of patients, the host's immune response is likely critical to the disease pathogenesis.

Drug reactions account for over two thirds of AIN cases. Although associations with many different drugs have been reported, the most frequent culprits include β-lactam antibiotics, rifampin, sulfonamides, diuretics, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs. In the past, the major cause of drug-induced AIN was methicillin, which caused disease in up to one in five patients, but this antibiotic is no longer used in the United States. Nonetheless, the incidence of drug-induced AIN is rising overall because of increasing drug use, especially in the older population.

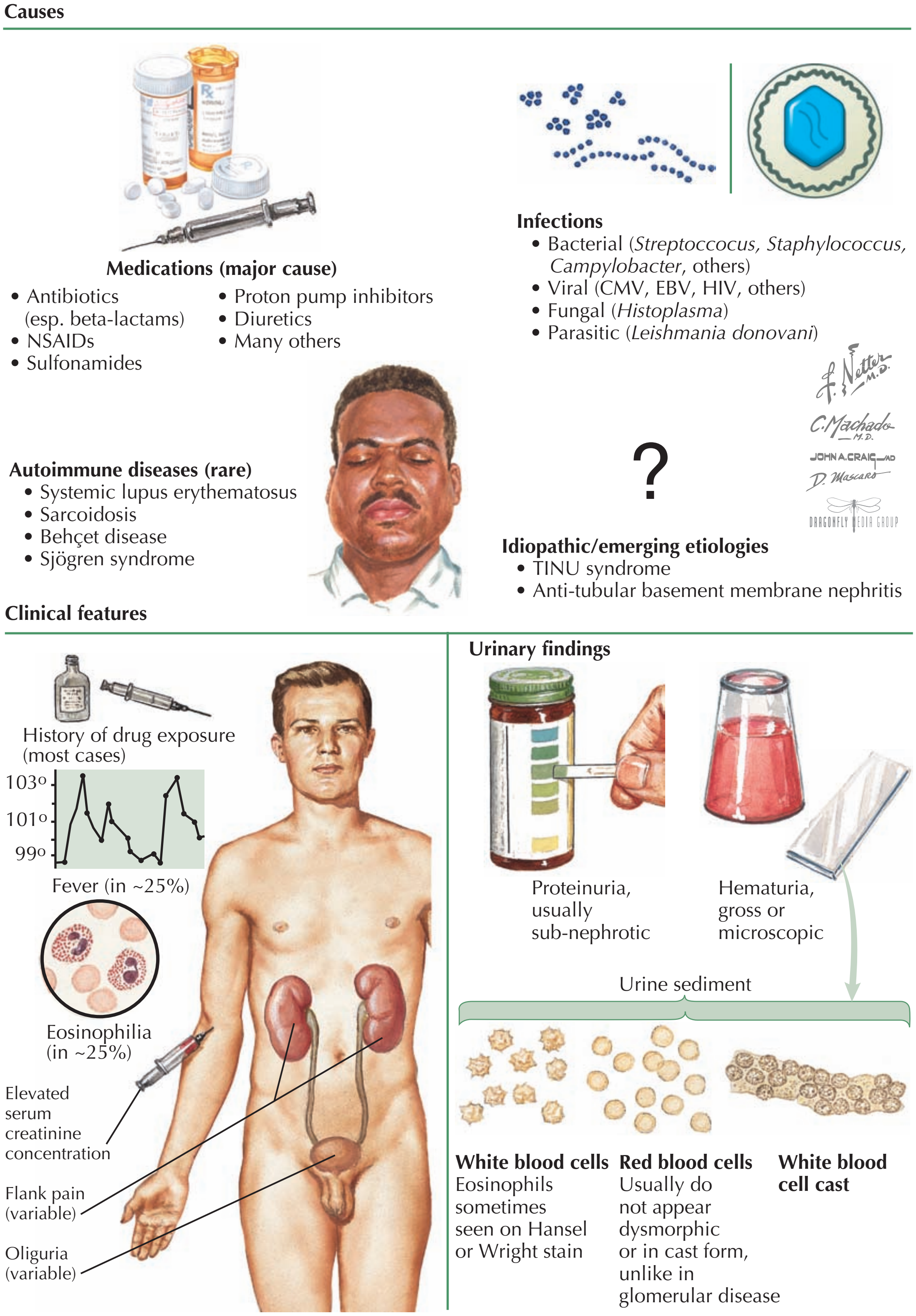
Many drugs cause disease by inciting a hypersensitivity-type reaction. β-lactams, for example, can serve as haptens by attaching to proteins on the tubular basement membrane, and forming an antigen that triggers a T-cell response. NSAIDs, however, appear to trigger disease through a largely nonallergic mechanism. Although the exact mechanism is unknown, it has been hypothesized that selective suppression of renal cyclooxygenase enzymes leads to increased metabolism of arachidonic acids toward leukotrienes, which trigger an immune response. NSAIDs may also infrequently induce a hypersensitivity-type response.

Infections account for 15% of AIN cases, and responsible agents can include bacteria (e.g., *Campylobacter*, *Salmonella*, *Streptococcus*, *Staphylococcus*, *Escherichia coli*, *Brucella*), viruses (e.g., cytomegalovirus, Epstein-Barr virus, HIV, herpes simplex virus), fungi (e.g., *Histoplasma*), and parasites (e.g., *Leishmania donovani*). Such agents can induce inflammation either through direct invasion of the renal parenchyma or through activation of the immune system in remote organs with collateral tubulointerstitial involvement. Infectious agents remain an important cause of AIN in developing nations.

Autoimmune diseases account for 10% of AIN cases, and responsible diseases include systemic lupus erythematosus, sarcoidosis, Behçet disease, and Sjögren syndrome.

The remaining AIN cases are considered idiopathic; however, antitubular basement membrane (TBM) nephritis and tubulointerstitial nephritis/uveitis (TINU) syndrome are now recognized as two causes of previously "idiopathic" AIN. Anti-TBM nephritis usually occurs in early childhood and results from circulating anti-TBM antibodies that target the proximal tubular basement membrane. TINU syndrome was first described in the 1970s, and a small number of cases has been reported since that time. The pathogenesis is unknown but likely immune-mediated.

Causes and Clinical Features of Acute Interstitial Nephritis


Causes
Medications (major cause)
• Antibiotics (esp. beta-lactams)
• NSAIDs
• Sulfonamides
• Proton pump inhibitors
• Diuretics
• Many others
Infections
• Bacterial (Streptoccocus, Staphylococcus, Campylobacter, others)
• Viral (CMV, EBV, HIV, others)
• Fungal (Histoplasma)
• Parasitic (Leishmania donovani)
Autoimmune diseases (rare)
• Systemic lupus erythematosus
• Sarcoidosis
• Behçet disease
• Sjögren syndrome
?
Idiopathic/emerging etiologies
• TINU syndrome
• Anti-tubular basement membrane nephritis
F. Netter M.D.
C. Machado M.D.
JOHN A. CRAIG AD
D. Mascaro
DRAGONFLY MEDIA GROUP
Clinical features
History of drug exposure (most cases)
103°
101°
99°
Fever (in ~25%)
Eosinophilia (in ~25%)
Elevated serum creatinine concentration
Flank pain (variable)
Oliguria (variable)
Urinary findings
Proteinuria, usually sub-nephrotic
Hematuria, gross or microscopic
Urine sediment
White blood cells
Eosinophils sometimes seen on Hansel or Wright stain
Red blood cells
Usually do not appear dysmorphic or in cast form, unlike in glomerular disease
White blood cell cast

PRESENTATION AND DIAGNOSIS

Acute interstitial nephritis typically manifests as AKI following the recent introduction of a new medication. Eighty percent of patients develop symptoms within 3 weeks of drug introduction, although there can be a latent period of several months following onset of NSAID use. The AKI can manifest either as oliguria or as an asymptomatic elevation in serum creatinine concentration noted on routine serum chemistries. In classic descriptions, the renal injury is accompanied by the triad of fever, rash, and eosinophilia; however, this picture emerged when the major pathogenetic agent was methicillin, which often triggered a hypersensitivity-type reaction. At present, largely because of the growing incidence of NSAID-related AIN, allergic symptoms are less consistent. Fever, rash, and eosinophilia are each seen in about 15% to 25% of patients, and the entire triad is seen in only 10%. In addition to these variable allergic symptoms, a fraction of patients

ACUTE INTERSTITIAL NEPHRITIS
(Continued)

may experience flank pain, gross hematuria, or both. Flank pain likely represents distention of the renal capsule secondary to interstitial edema. Hypertension and gross edema are uncommon.

Urinalysis often reveals proteinuria, which is mild on quantitative analysis (i.e., <2 g/day) and reflects impaired tubular reabsorption of filtered proteins. Nephrotic-range proteinuria may rarely be seen in those cases where NSAID exposure causes both AIN and minimal change disease (see Plate 4-8). Microscopic analysis of urine often reveals white blood cells (WBCs), red blood cells (RBCs), and WBC casts. These findings can facilitate the distinction from acute tubular necrosis (ATN, see Plate 4-3), which is the most common cause of intrarenal AKI and typically features a bland sediment or epithelial cell casts. In addition, the lack of RBC casts or dysmorphic RBCs facilitates the distinction from acute glomerulonephritis. Finally, the presence of proteinuria and an active sediment can be used to exclude prerenal state, which may also occur in the setting of NSAID use secondary to interference with tubuloglomerular feedback (see Plate 3-18).

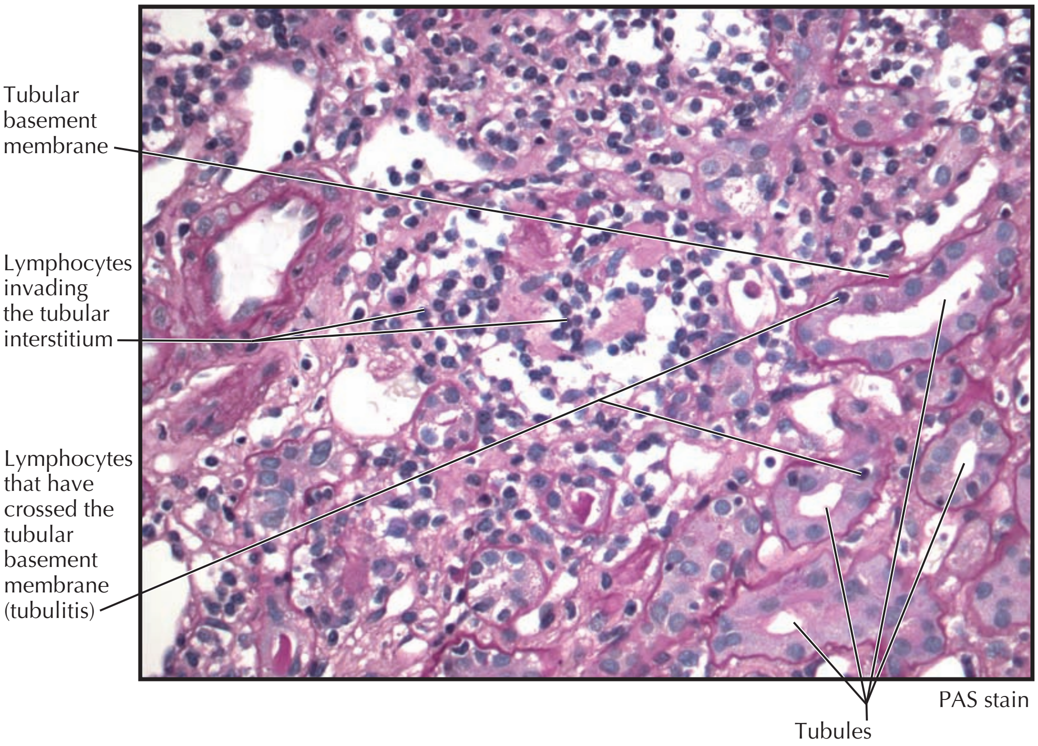
Eosinophiluria (defined as eosinophils >1% of WBCs seen in urine) occurs in some patients with AIN but can only be detected using special stains, such as Hansel or Wright stains. Moreover, eosinophiluria may be a nonspecific finding because it can also occur in atheroembolic renal disease, urinary tract infections, and some glomerulonephritides. Thus its diagnostic utility is unclear.

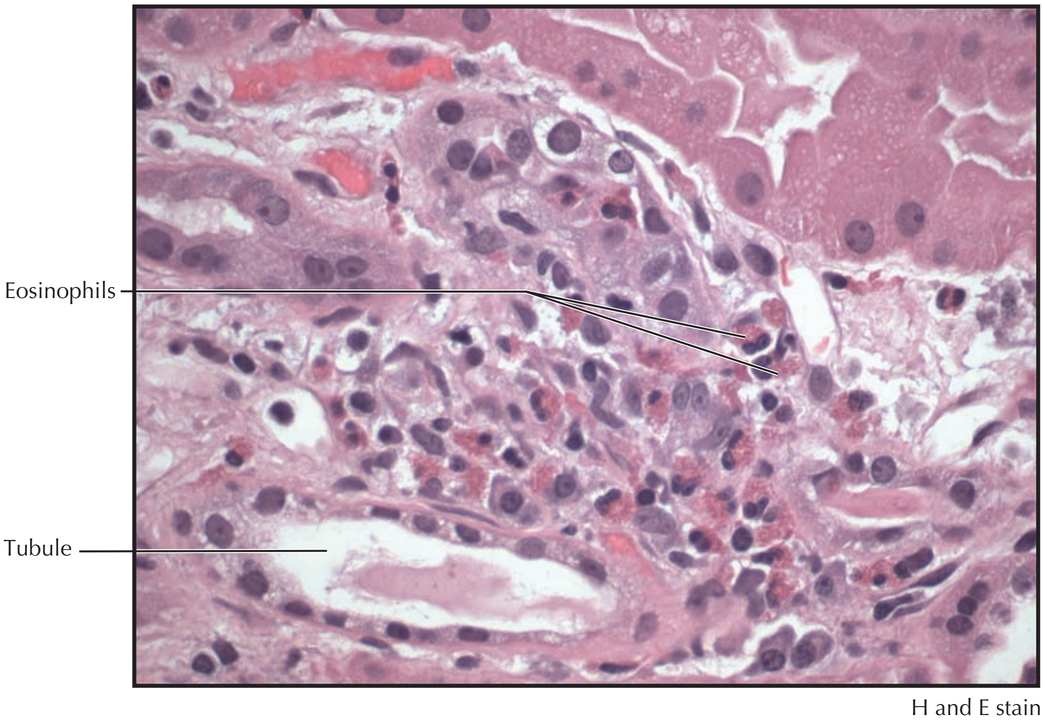
Renal ultrasound results are often normal. Diffuse cortical echogenicity secondary to interstitial inflammation has been described, but no studies have validated the sensitivity or specificity of this finding. Gallium scan has been proposed as a potentially useful diagnostic tool. Gallium is a radioactive tracer that colocalizes with WBCs and has traditionally been used for the detection of abscesses. In acute interstitial nephritis, there is diffuse, bilateral uptake of gallium, which reflects the underlying inflammatory process. There are conflicting results, however, regarding the sensitivity and specificity of this procedure for the diagnosis of AIN. Thus it is seldom used in clinical practice.

The distinction between AIN or atheroembolic renal disease can sometimes be challenging because both may cause AKI with eosinophiluria and mild proteinuria, fevers, arthralgias, and rash. The rash in AIN, however, is typically maculopapular and erythematous, whereas atheroembolic disease usually causes livedo reticularis or mottled, violaceous toes. Atheroembolic disease is also more likely in certain high-risk populations, such as elderly patients with vascular disease who have recently undergone an open surgical or percutaneous procedure.

Biopsy is required to confirm the diagnosis of AIN. It is typically performed in patients with unexplained AKI and a cellular urine sediment who do not quickly respond to termination of potentially causative drugs. On light microscopy, AIN features a lymphocyte-predominant interstitial infiltrate typically accompanied by edema. The presence of eosinophils suggests a drug-induced, allergic cause. Occasionally, granulomas may also be noted. Tubular injury may occur, with passage of lymphocytes across the tubular basement membrane (“tubulitis”), but the glomeruli and blood vessels are typically spared. Inflammation is typically much more prominent in the renal cortex than in the medulla.

HISTOPATHOLOGIC FINDINGS OF ACUTE INTERSTITIAL NEPHRITIS


Tubular basement membrane
Lymphocytes invading the tubular interstitium
Lymphocytes that have crossed the tubular basement membrane (tubulitis)
Tubules
PAS stain



TREATMENT

Initial treatment for acute interstitial nephritis includes discontinuation of all potential offending drugs and eradication of any potential infections. Once an offending drug has been identified it should never be reintroduced because it will reliably cause future episodes of interstitial nephritis.

In addition, there is recent evidence that early steroid administration in drug-induced disease leads to faster and greater recovery of renal function. Thus, in the absence of any contraindications, a limited course of corticosteroids may be considered.

PROGNOSIS

Most patients will experience complete recovery of renal function. A minority will progress to end stage renal disease and require renal replacement therapy. The duration of renal failure, rather than the peak serum creatinine concentration, appears to be the most important indicator of eventual recovery. Some data also suggest patients of advanced age may have a less favorable prognosis.

CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis can be divided into acute and chronic forms. Acute interstitial nephritis (AIN, see Plate 4-28) is typically associated with more severe insults, which cause a rapid decline in renal function and significant tubulointerstitial inflammation.

In contrast, primary chronic tubulointerstitial nephritis (CTIN) results either from untreated AIN or more commonly, a milder renal injury that takes a more indolent course. Instead of inflammation, there is tubulointerstitial fibrosis and scarring, with a slow deterioration of renal function. Although both acute and chronic forms have overlapping causes, they can be considered separate renal diseases because of their unique pathophysiologies.

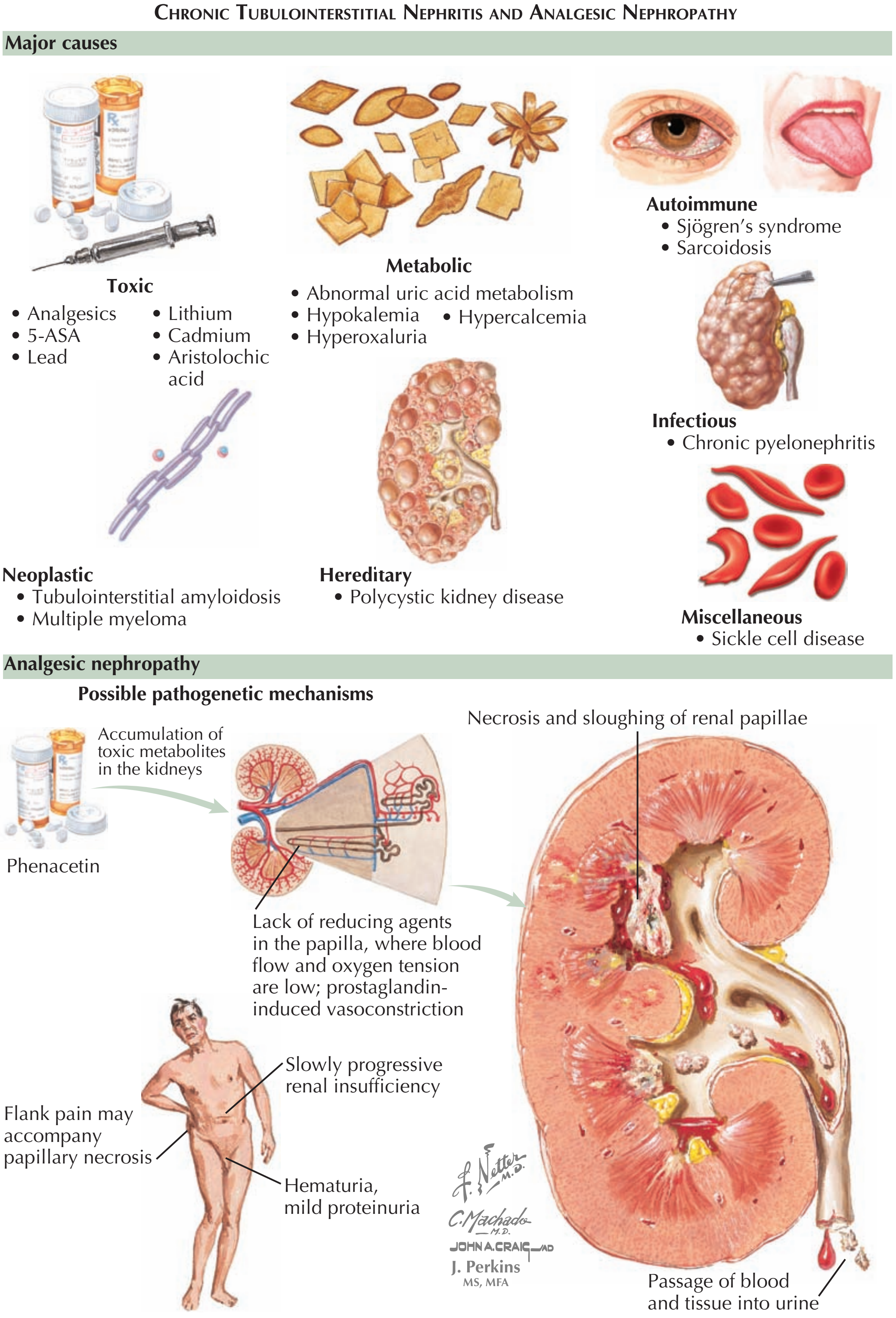
Between 10% to 20% of cases of end-stage renal disease (ESRD) worldwide result from primary CTIN, a number that continues to grow as an increasing number of causes are identified.

PATHOPHYSIOLOGY

CTIN can occur as either a primary or secondary phenomenon. In primary CTIN, the initial injury affects the tubulointerstitium without glomerular or vascular involvement. As the tubulointerstitial damage progresses, however, glomerular sclerosis and arteriolar thickening often develop. One possible mechanism to explain this phenomenon is tubuloglomerular feedback. In tubuloglomerular feedback, tubular damage results in decreased proximal reabsorption of electrolytes, which leads to a high solute load at the macula densa and resultant vasoconstriction of the afferent arteriole. This vasoconstriction causes glomerular ischemia that, if persistent, can result in glomerulosclerosis. Another explanation of the secondary glomerular damage seen in primary CTIN is "renal ablation nephropathy," a theory which speculates that glomerulosclerosis results from a loss of renal mass caused by interstitial scarring.

In secondary CTIN, in contrast, tubulointerstitial damage occurs in the setting of a primary glomerular or vascular insult. The tubular disease is thought to occur because of a toxic effect of filtered proteins on tubular cells. It is also thought that ischemia distal to sclerotic glomeruli causes tubular injury. Once injured, these tubular cells express adhesion molecules and elaborate cytokines and growth factors that cause interstitial inflammation and fibrosis. Thus secondary CTIN is a pathologic endpoint for many renal processes and is not considered a primary renal disease.

There are numerous causes of primary CTIN, and in general these are divided into seven major classes: toxic, metabolic, autoimmune, infectious, neoplastic, hereditary, and miscellaneous. Toxin-induced insults are the most common cause of CTIN, and the agents most often implicated are analgesics, 5-ASA, lead, lithium, cadmium, and aristolochic acid. Metabolic causes include abnormal uric acid metabolism, hypokalemia, hypercalcemia, and hyperoxaluria. Autoimmune causes often include Sjögren syndrome and sarcoidosis. The major infectious, neoplastic, hereditary, and miscellaneous causes include chronic pyelonephritis; multiple myeloma (see Plate 4-53) and tubulointerstitial amyloidosis (see Plate 4-47); polycystic kidney disease; and sickle cell disease, respectively.


CHRONIC TUBULOINTERSTITIAL NEPHRITIS AND ANALGESIC NEPHROPATHY

Major causes
Toxic
• Analgesics
• 5-ASA
• Lead
• Lithium
• Cadmium
• Aristolochic acid
Metabolic
• Abnormal uric acid metabolism
• Hypokalemia
• Hypercalcemia
• Hyperoxaluria
Autoimmune
• Sjögren's syndrome
• Sarcoidosis
Infectious
• Chronic pyelonephritis
Neoplastic
• Tubulointerstitial amyloidosis
• Multiple myeloma
Hereditary
• Polycystic kidney disease
Miscellaneous
• Sickle cell disease
Analgesic nephropathy
Possible pathogenetic mechanisms
Accumulation of toxic metabolites in the kidneys
Phenacetin
Lack of reducing agents in the papilla, where blood flow and oxygen tension are low; prostaglandin-induced vasoconstriction
Necrosis and sloughing of renal papillae
Flank pain may accompany papillary necrosis
Slowly progressive renal insufficiency
Hematuria, mild proteinuria
Passage of blood and tissue into urine
F. Netter M.D.
C.Machado M.D.
JOHN A.CRAIG AD
J. Perkins MS, MFA

Analgesic nephropathy is one of the most significant causes of CTIN. It was first described in the 1950s, when a series of 44 CTIN cases and 22 cases of papillary necrosis were found to be associated with chronic analgesic use. At its peak, analgesic nephropathy was estimated to cause approximately 1% of cases of ESRD in the United States and as many as 20% of cases of ESRD in Europe and Australia.

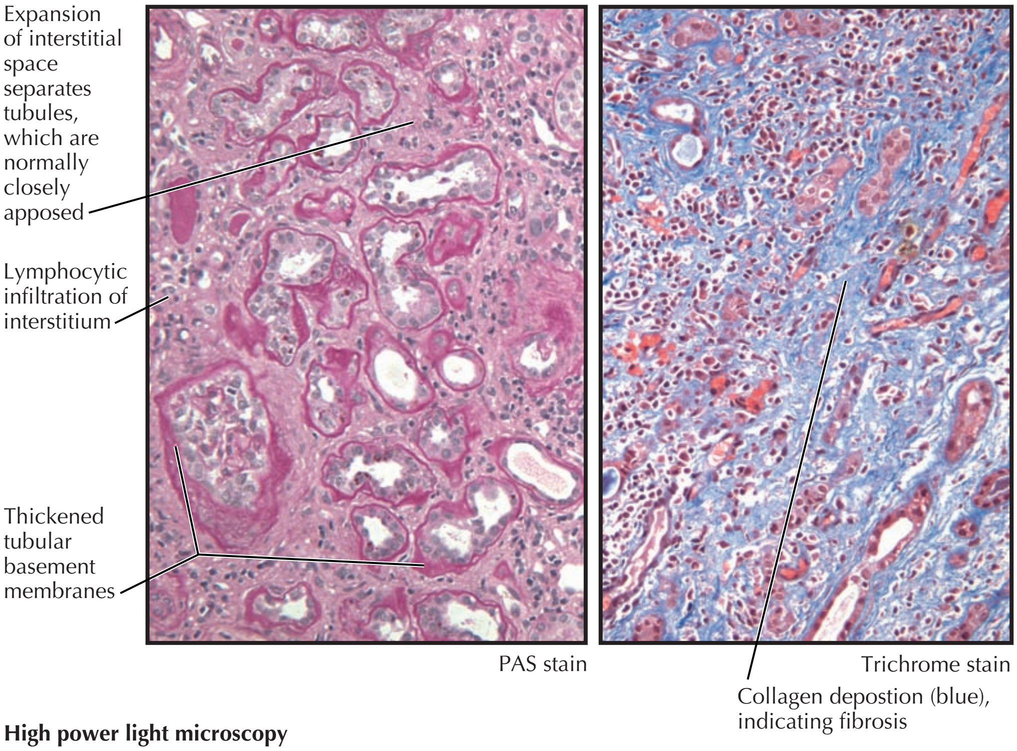
The responsible analgesics often included a mixture of different substances, including phenacetin, acetaminophen (phenacetin's major metabolite), and other agents such as NSAIDs, codeine, aspirin, and caffeine. Although there was no direct evidence that phenacetin was the main agent responsible for disease, multiple case series aroused enough suspicion to cause this substance to be banned in Europe in the 1970s and in the United States in 1983. Following this ban, the incidence of analgesic nephropathy has been reported to have decreased; however, variable reporting and difficulties in diagnosis have made this hard to confirm. Moreover, experimental models and clinical case series have illustrated the toxic potential of other analgesics, including acetaminophen, NSAIDs, and aspirin.

Analgesic nephropathy (AN) can serve as a model for the pathogenesis of CTIN. Although the exact mechanism remains incompletely understood, it appears that toxic metabolites are reabsorbed by tubular cells and accumulate. When there is an inadequate supply of reducing agents, these metabolites cause oxidative

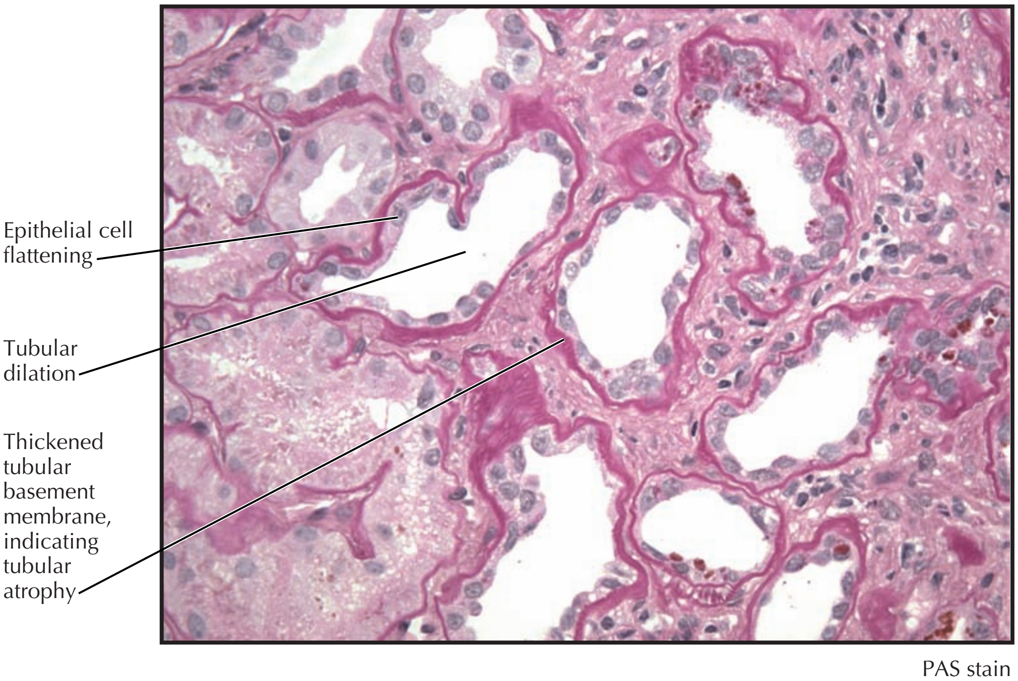
CHRONIC TUBULOINTERSTITIAL NEPHRITIS *(Continued)*

HISTOPATHOLOGIC FINDINGS OF CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Low power light microscopy


Expansion of interstitial space separates tubules, which are normally closely apposed
Lymphocytic infiltration of interstitium
Thickened tubular basement membranes
PAS stain
Trichrome stain
Collagen depostion (blue), indicating fibrosis

High power light microscopy


Epithelial cell flattening
Tubular dilation
Thickened tubular basement membrane, indicating tubular atrophy
PAS stain

injury. This injury is most pronounced in the renal papilla, where blood flow and oxygen tension are low. When analgesic combinations include an inhibitor of prostaglandin synthesis, such as aspirin, the resulting renal vasoconstriction can predispose the papilla to ischemia and ultimately necrosis. Although papillary necrosis is characteristic of analgesic nephropathy it is not specific because it can also occur in diabetes (see Plate 4-45), sickle cell anemia, urinary tract obstruction (see Plate 6-1), and renal tuberculosis (see Plate 5-10).

Indeed, the tubular accumulation of toxic substances appears to be the major pathogenetic mechanism by which many other substances cause CTIN. Other mechanisms, however, may also be responsible. In chronic obstructive pyelonephritis, for example, tubulointerstitial inflammation and scarring is caused by recurrent infections superimposed on diffuse or localized obstructive lesions. In urate nephropathy, deposition of monosodium urate crystals in the distal tubules and collecting ducts induces formation of tophi, which are surrounded by foreign body giant cells and other mononuclear cells that cause localized fibrosis.

PRESENTATION AND DIAGNOSIS

Because of its effects on glomeruli described previously, CTIN is typically associated with a slow but progressive decline of GFR. Early in the course of disease, however, there is mild (if any) effect on blood pressure and minimal to absent edema on physical examination. Urinalysis with microscopy shows no signs of inflammation and minimal proteinuria (often <1 g/day). In cases of analgesic nephropathy, patients may have flank pain or hematuria associated with papillary necrosis. Other clinical features may be extrarenal and reflect the underlying process.

If the tubular damage is more advanced, patients may begin to exhibit evidence of renal tubular dysfunction, including polyuria, renal tubular acidosis (see Plate 3-25), and even the renal Fanconi syndrome (see Plate 4-64), which includes salt wasting, glucosuria, aminoaciduria, phosphaturia, hypercalciuria, low molecular weight proteinuria, and polyuria.

Imaging with renal ultrasound can reveal evidence of cortical scarring, such as a bilateral reduction in kidney size, irregular cortical borders, and hypoechoic segments; however, these findings tend to occur late in the course of disease. Other imaging tests are not routinely performed when diagnosing CTIN; however, if abdominal computed tomography is performed, it may reveal renal papillary calcifications, which are highly specific for analgesic-induced CTIN.

Because clinical and laboratory findings are often ambiguous, the definitive diagnosis of CTIN often requires renal biopsy. If there is evidence of cortical scarring on ultrasound, however, a renal biopsy is often not performed because these patients have irreversible kidney disease and are at higher risk for bleeding complications. If a biopsy is performed, the major pathologic features of CTIN include atrophied, dilated tubules with flattened epithelial cells and thickened basement membranes. The interstitial compartment reveals fibrosis and scarring, with varying degrees of leukocytic infiltration depending on the severity and persistence of the disease. This infiltrate predominantly consists of lymphocytes, macrophages, or B cells. Depending on the chronicity of renal injury, a variable degree of glomerulosclerosis and/or arteriolar thickening may be seen.

Additional findings may be present depending on the specific cause of disease, such as papillary necrosis in analgesic nephropathy, distal tubular urate crystal deposition and tophi in urate nephropathy, tubular (myeloma) casts in multiple myeloma, tubular microcysts in lithium toxicity, and proximal tubular vacuolization in hypokalemic nephropathy.

TREATMENT

The treatment of CTIN focuses on identifying and addressing correctable risk factors, such as medication use, metabolic abnormalities, and infections. Except in cases of neoplastic and hereditary disease, renal dysfunction is often reversible if the inciting agent is removed early enough. Patients with a significant amount of inflammation on biopsy may be candidates for immunosuppression, although no randomized control trials have supported its use. The two most important risk factors for progression to end-stage renal disease are the serum creatinine concentration at the time of diagnosis and the extent of tubulointerstitial scarring at the time of biopsy.

THROMBOTIC MICROANGIOPATHY

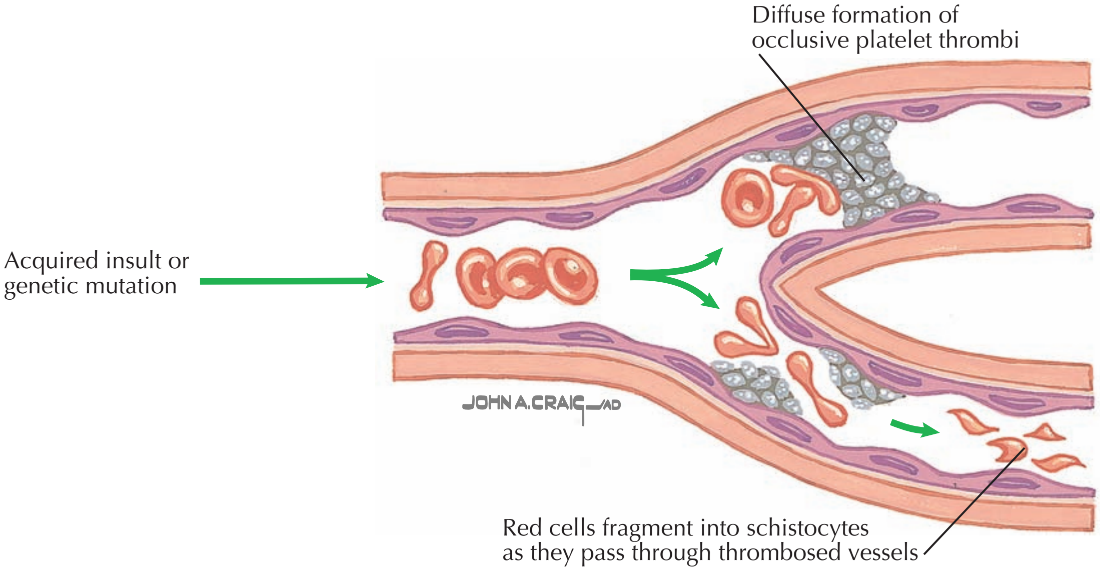
The thrombotic microangiopathies are a group of disorders that share common clinical and histopathologic features. Two major types are known as thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). TTP is characterized by systemic formation of occlusive microvascular thrombi composed primarily of platelets, which cause organ ischemia that is rapidly fatal if untreated. In HUS the microvascular thrombi are primarily localized to the kidney, with acute kidney injury being the principal clinical feature.

The major laboratory findings of both TTP and HUS include thrombocytopenia, resulting from platelet consumption, and microangiopathic hemolytic anemia (MAHA), resulting from the mechanical stress on erythrocytes as they pass through the narrow, thrombosed vessels.

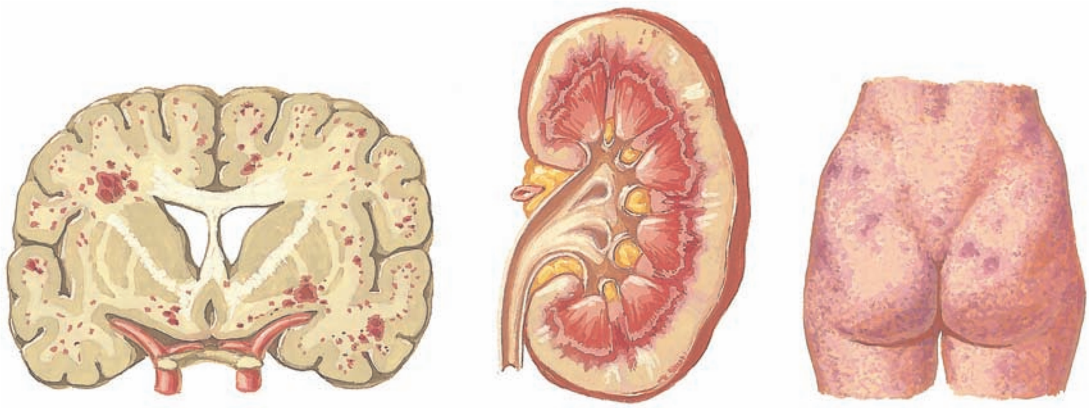
The distinction between TTP and HUS is often made based on the organ system most affected. As stated previously, HUS is said to feature prominent renal dysfunction, whereas TTP is said to feature more systemic abnormalities, including neurologic findings. In some cases, however, both disease processes can be associated with both renal and neurologic symptoms. Thus a simple classification scheme based on symptoms is often unreliable. Recent research, however, has helped elucidate the actual mechanisms that underlie HUS and TTP, which may eventually permit rapid differentiation and focused treatment irrespective of the presenting symptoms.

General Features of Thrombotic Microangiopathy

Pathogenesis


Diffuse formation of occlusive platelet thrombi
Acquired insult or genetic mutation
JOHN A.CRAIG—AD
Red cells fragment into schistocytes as they pass through thrombosed vessels

Clinical manifestations

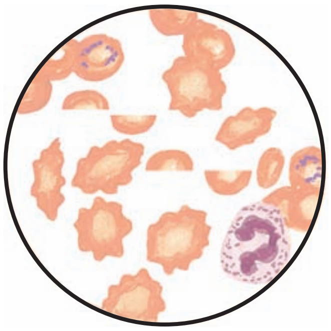


Neurologic symptoms
coma, seizures, focal deficits
(related to thrombosis
of cerebral vasculature)

Acute kidney injury
(related to thrombosis
of renal vasculature)

Purpura
(related to thrombosis
of dermal vasculature)

Laboratory findings



- Microangiopathic hemolytic anemia (schistocytes seen on smear)
- Elevated serum LDH
- Thrombocytopenia

PATHOPHYSIOLOGY

Hemolytic Uremic Syndrome. HUS may occur in multiple settings, but more than 90% of cases (termed "typical HUS") are related to infection with bacteria that produce Shiga-like toxins (Stx). In a small number of patients infected with such bacteria, Stx enters the general circulation and binds to receptors on glomerular endothelial cells. The toxin causes extensive endothelial damage and promotes increased expression of cytokines, chemokines, and cell adhesion molecules. The resulting inflammation triggers platelet activation and diffuse thrombosis of the renal microvasculature. Bacteremia is neither necessary for this process nor commonly observed.

The incidence is highest in children under 5 years of age, among whom there are 6.1 cases per 100,000 persons per year. The major pathogen is Stx-producing *E. coli O157:H7*, but other *E. coli* serotypes may also be responsible. Infection with these pathogens results from ingestion of contaminated food (usually undercooked ground beef or dairy) or water. Because these pathogens also cause diarrhea in a majority of cases, typical HUS is also known as diarrhea-associated (D+) HUS. The distinct age-related incidence of this condition could be explained by a greater affinity of glomerular endothelial cells for Stx in young children.

Atypical HUS (also called D−HUS because it lacks a diarrhea prodrome), in contrast, may occur for numerous reasons. In some patients, it appears to reflect dysregulated activation of the complement system, which leads to endothelial damage and platelet aggregation. Affected individuals have been found to possess mutations in genes encoding inhibitors of the alternative, C3b-mediated complement pathway. These inhibitors include factor H, factor C, factor I, factor B, and membrane cofactor protein (MCP). If severe enough, these mutations cause spontaneous and recurrent activation of the complement system starting in childhood. The reason for the particular susceptibility of the renal circulation is not clear; however, it has been postulated that the presence of endothelial fenestrations in the glomerulus increases exposure of the circulating factors to subendothelial proteins, which may serve as a focus for complement activation. Patients with such mutations often have a family history of similar events and are therefore said to have a "familial" form of atypical HUS.

THROMBOTIC MICROANGIOPATHY

(Continued)

The remaining patients with atypical HUS have a “sporadic” form that is either idiopathic or related to triggers, such as pregnancy, infection (e.g., *Streptococcus pneumoniae*), and certain drugs (e.g., quinine, cyclosporine, tacrolimus). The mechanisms are probably diverse. Quinine, for example, appears to modify an epitope on platelets, leading to binding of antibodies. *S. pneumoniae* is believed to produce an enzyme that can expose a cryptic antigen on erythrocytes, platelets, and glomeruli endothelial cells, leading to an autoimmune response. Finally, it is possible that some patients have complement mutations that do not cause thrombosis under normal physiologic conditions, but which lead to thrombosis in response to the endothelial damage associated with certain triggers.

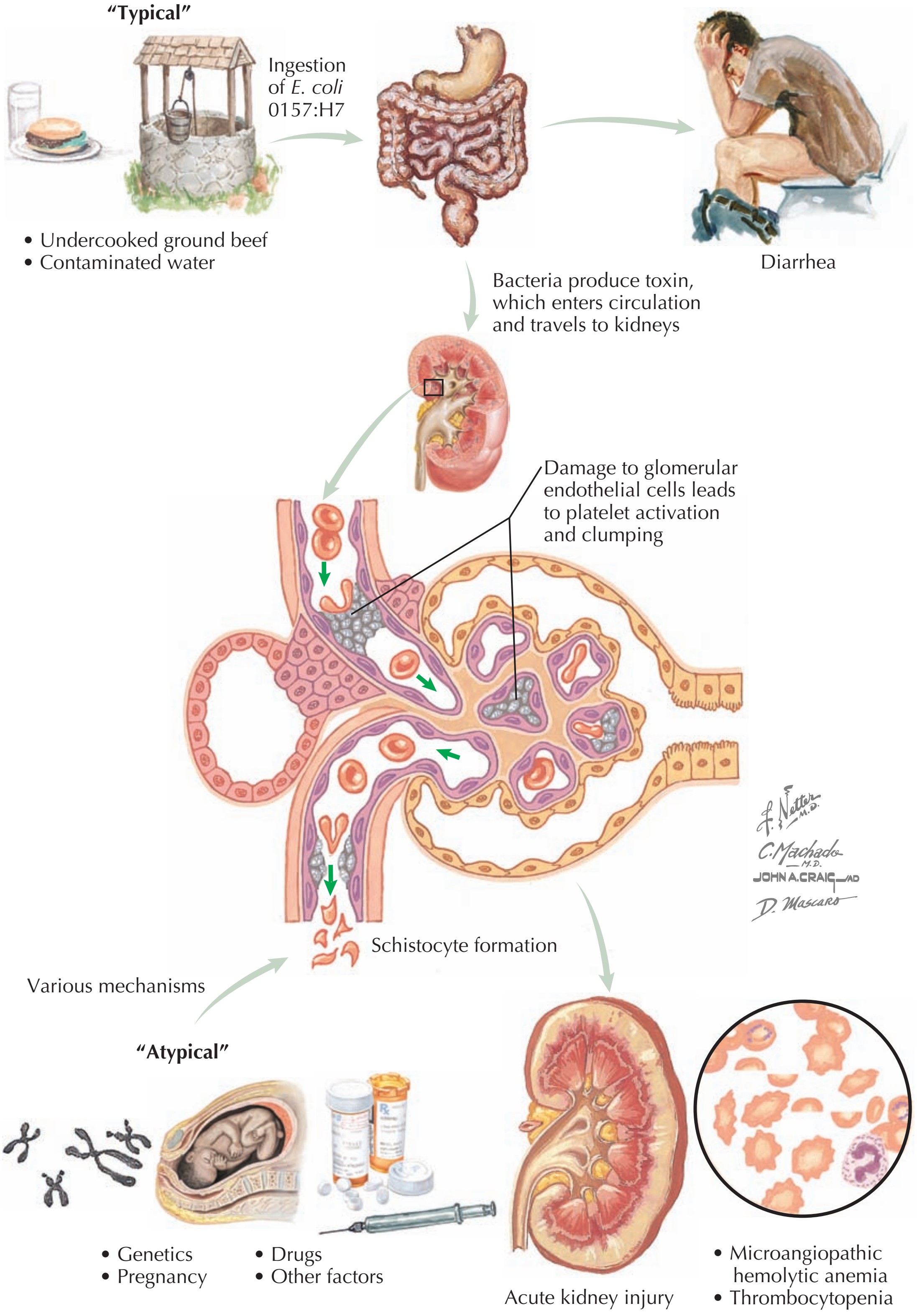
Thrombotic Thrombocytopenic Purpura. TTP generally involves more diffuse thrombus formation than HUS. It also occurs in both familial and sporadic forms. The main pathogenetic factor appears to be a deficiency of a normal plasma enzyme, ADAMTS13 (A Disintegrin and Metalloprotease with ThromboSpondin type 1 domains, member 13), that is required for processing of von Willebrand factor (vWF) multimers. In normal conditions, endothelial cells constitutively secrete a range of vWF multimers, including unusually large multimers (ULvWF). These unusually large vWF multimers have a much higher platelet binding affinity than the smaller multimers, but under normal conditions they undergo cleavage by ADAMTS13 immediately after release. In TTP, ADAMTS13 may be absent or dysfunctional, and the resulting circulation of ULvWF can cause formation of platelet-rich thrombi.

The familial form of TTP, known as Upshaw-Schulman syndrome, accounts for a very small fraction of cases. In this case, there is near total absence of the ADAMTS13 protein. The disease often appears shortly after birth, with subsequent relapses occurring in the setting of infection, pregnancy, or other physiologic stressors, presumably because of increased ULvWF multimer production. In some cases, however, the first episode may not occur until these stressors are experienced in adulthood. Inheritance follows an autosomal recessive pattern.

A sporadic, acquired form of TTP accounts for a majority of cases and typically affects adults. Most cases appear to reflect abnormal production of anti-ADAMTS13 IgG autoantibodies, which either promote clearance of ADAMTS13 or neutralize its binding site. It is not known why certain individuals develop these antibodies, which often disappear after symptoms resolve.

Secondary TTP may occur in susceptible individuals, such as in the setting of pregnancy. It is not clear why certain triggers cause systemic platelet thrombosis; however, it is possible that ongoing endothelial stress leads to an overwhelming increase in ULvWF secretion.

PATHOLOGY AND CLINICAL FEATURES OF HEMOLYTIC UREMIC SYNDROME



“Typical”
Ingestion of *E. coli* 0157:H7
• Undercooked ground beef
• Contaminated water
Diarrhea
Bacteria produce toxin, which enters circulation and travels to kidneys
Damage to glomerular endothelial cells leads to platelet activation and clumping
Schistocyte formation
Various mechanisms
“Atypical”
• Genetics
• Pregnancy
• Drugs
• Other factors
Acute kidney injury
• Microangiopathic hemolytic anemia
• Thrombocytopenia
F. Netter M.D.
C. Machado M.D.
JOHN A. CRAIG AD
D. Mascaro

PRESENTATION AND DIAGNOSIS

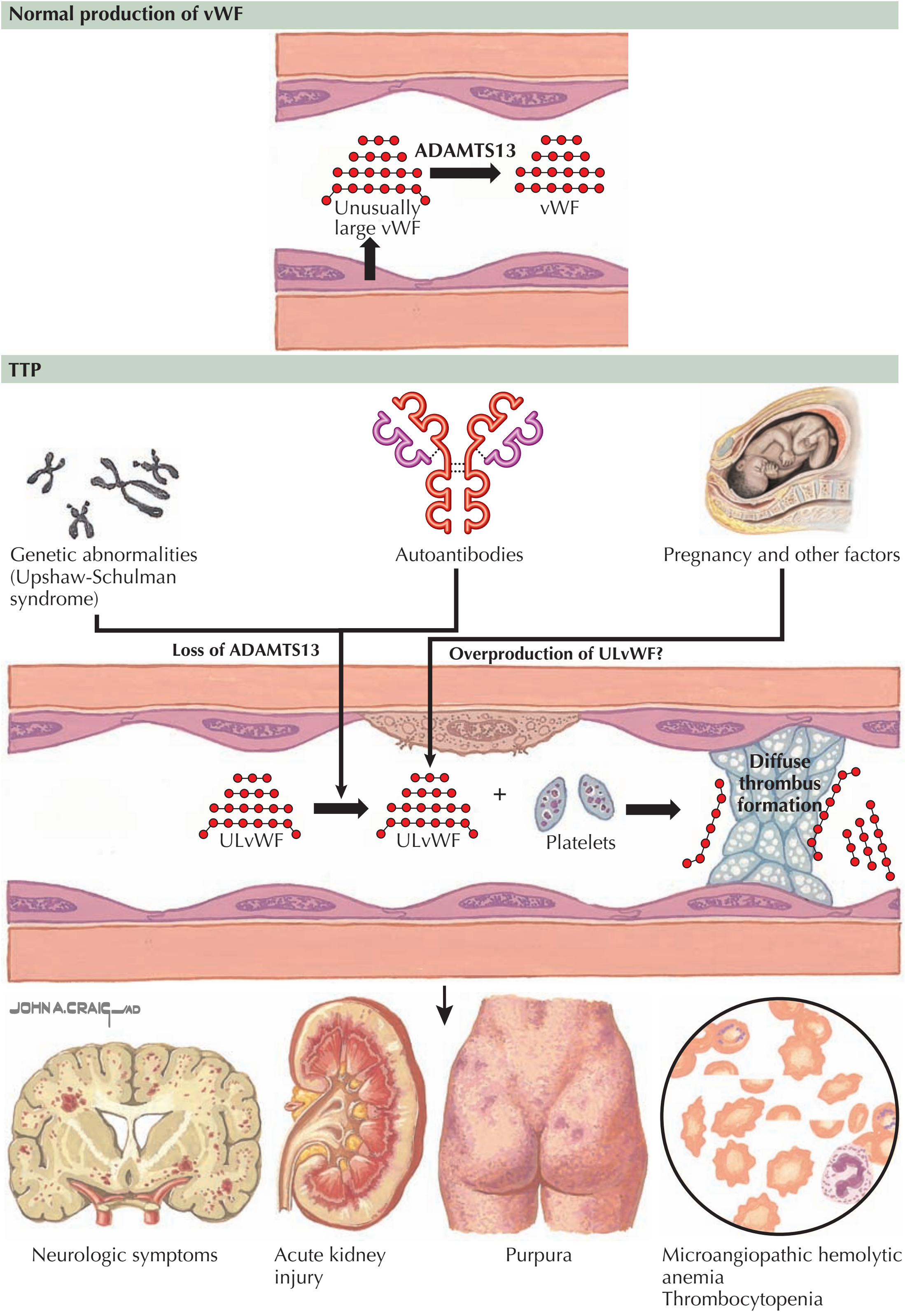
Patients with either TTP or HUS can have acute kidney injury, manifesting as oliguria, fatigue, nausea, and vomiting; fluctuating neurologic symptoms, such as seizures, focal deficits, or even coma; or both. In addition, patients may have fever and purpura, although overt bleeding is unusual. These symptoms are often sudden, but in up to one fourth of patients they can be present for weeks before presentation.

On further investigation, patients are found to have thrombocytopenia, with platelet counts often below 20,000/µL; MAHA, evidenced as numerous schistocytes on a peripheral blood smear; and elevated lactate dehydrogenase (LDH). Serum creatinine concentration is elevated if there is renal involvement, and urinalysis may be normal or reveal RBCs and mild proteinuria. Prothrombin and partial thromboplastin times, as well as levels of individual clotting factors, should be normal in both TTP and HUS and can help facilitate the distinction from disseminated intravascular coagula-tion (DIC).

THROMBOTIC MICROANGIOPATHY

(Continued)

Pathophysiology and Clinical Features of Thrombotic Thrombocytopenic Purpura



The laboratory findings of thrombocytopenia, elevated LDH, and schistocytosis in the absence of another apparent cause (such as DIC, malignant hypertension, or recent stem cell transplantation) are sufficient to make the diagnosis of TTP or HUS.

TREATMENT

The definitive distinction between TTP and HUS is neither possible nor necessary in the acute setting. In all patients, the drug regimen should be examined and potential precipitants stopped. Supportive care should focus on managing fluid and electrolyte status, treating hypertension, and offering dialysis, packed RBC transfusions, or antiepileptic drugs as needed. The indications for dialysis in TTP and HUS are the same as in other settings. Platelet transfusion should not be performed unless there is overt bleeding or an invasive procedure is required because it may precipitate the formation of additional thrombi.

Further management depends on patient characteristics and clinical findings.

Infants and young children with a recent history of bloody diarrhea, for example, likely have typical HUS and usually recover completely with supportive therapy alone. Plasma exchange/infusion and Shiga-toxin binding agents do not appear to improve outcomes. Antimotility agents and antibiotics may actually worsen the toxin-mediated damage. In most patients, hematologic markers will return to normal within 1 to 2 weeks.

Infants and young children without a recent history of bloody diarrhea could have typical HUS, atypical HUS, or Upshaw-Schulman syndrome. In this case, patients typically receive plasma infusions, which replace the missing factors in the hereditary conditions. Genetic testing should be performed to guide further management.

Older children and adults could have any form of TTP or HUS, and the distinction is often unclear at initial presentation. For example, adults with a recent history of bloody diarrhea could have typical HUS caused by *E. coli 0157:H7* infection or TTP with mesenteric ischemia. Likewise, the presence of a potential trigger for either secondary TTP or atypical HUS does not exclude the possibility of idiopathic TTP.

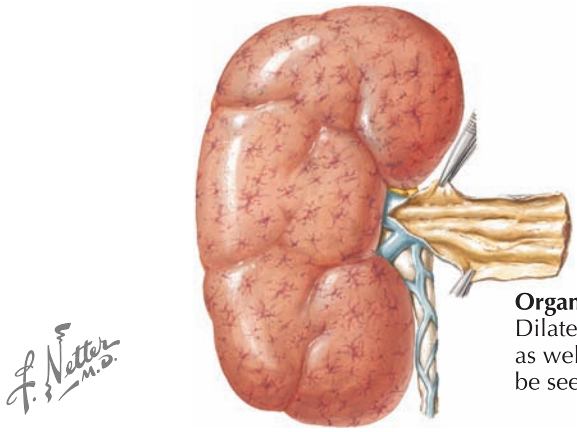
Thus plasma exchange should be offered to all older children and adults to remove possible ADAMTS13 autoantibodies. After the initiation of plasma exchange, symptoms and laboratory markers should improve within 1 to 3 days. If there is a lack of response, patients may be candidates for pharmacologic immunosuppression, which reduces the production of autoantibodies.

PROGNOSIS

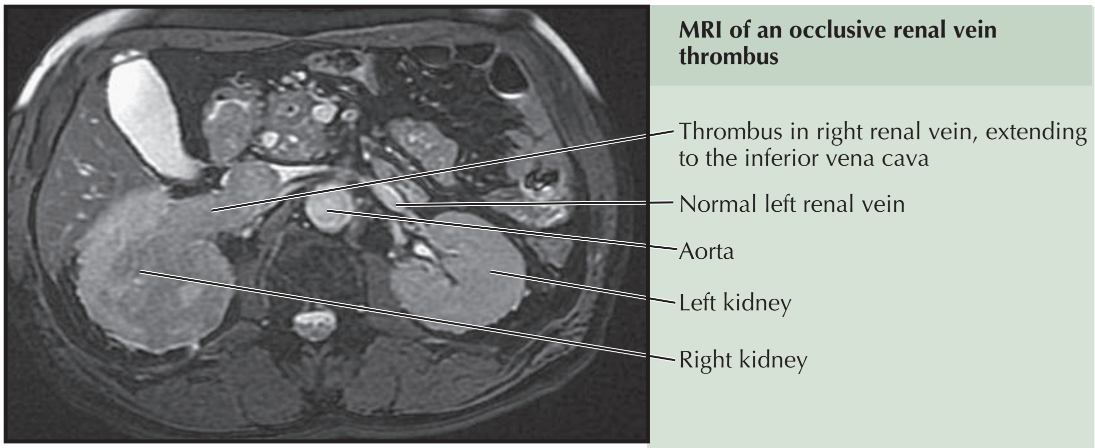
In children, the prognosis of typical HUS is excellent if appropriate supportive care is given, with most recovering normal renal function. All patients should undergo annual monitoring for late complications such as hypertension and mild proteinuria. Relapses are very rare. In familial D-HUS, the prognosis depends on the responsible mutation. For example, patients with complement factor H mutations may become dependent on plasma exchange. The possible role of complement cascade inhibitors such as eculizumab, an anti-C5 monoclonal antibody, is currently under investigation.

In adults, the prognosis of untreated TTP or HUS is extremely poor, with survival rates of only 10%. With plasma exchange, however, survival rates have improved to 80%, although relapses occur in one third of patients with TTP associated with ADAMTS13 autoantibodies. Chronic kidney disease generally does not occur in patients with ADAMTS13 autoantibodies; however, patients may report persistence of minor cognitive symptoms, such as poor concentration or memory.

RENAL VEIN THROMBOSIS

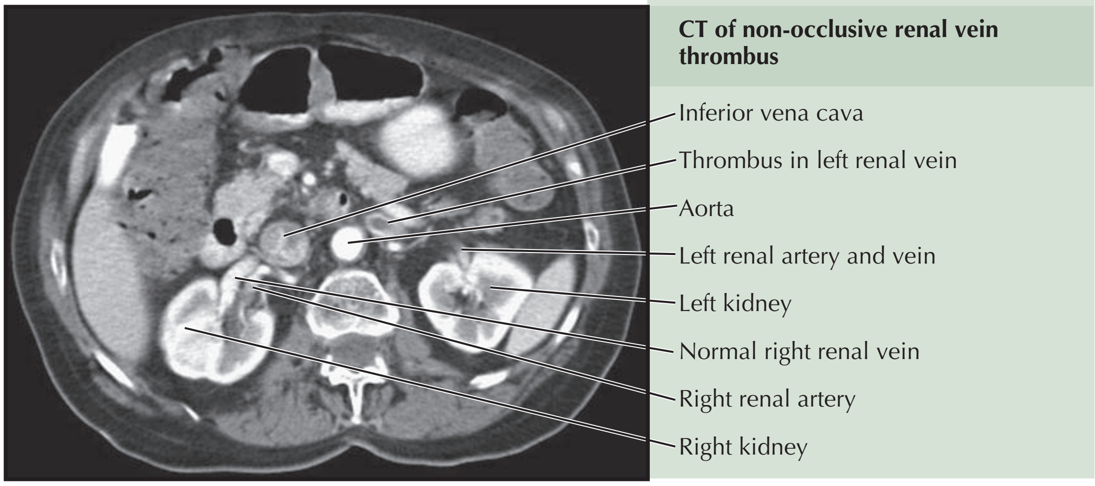


Organized thrombus in renal vein
Dilated vessels at parenchyma surface, as well as around the hilum, may be seen grossly.



MRI of an occlusive renal vein thrombus

Thrombus in right renal vein, extending to the inferior vena cava
Normal left renal vein
Aorta
Left kidney
Right kidney



CT of non-occlusive renal vein thrombus

Renal vein thrombosis (RVT) is a frequent complication among patients with nephrotic syndrome (see Plate 4-5). The overall prevalence in this population ranges from 5% to 60% in different series, and known risk factors include membranous nephropathy, heavy proteinuria (>10 g/day), and low serum albumin (<2 g/dL). Although it was once believed that RVTs caused nephrotic syndrome, the direction of causality is now known to be reversed.

RVTs may also occur in the setting of renal malignancy, renal transplant, steroid use, oral contraceptive use, renal trauma (including biopsies and other procedures), and hypovolemia.

PATHOPHYSIOLOGY

The pathophysiology of the hypercoagulable state in nephrotic syndrome is complex and controversial. Possible causes include the urinary loss of small molecular weight anticoagulants (antithrombin III, protein S) and fibrinolytics (plasminogen). In addition, however, the hepatic overproduction of proteins, which occurs in response to hypoalbuminemia, also leads to elevated concentrations of higher molecular weight procoagulants, such as factor V, factor VIII, and fibrinogen.

Platelet abnormalities may also play a role. First, there may be increased platelet activation because of associated systemic inflammation. Second, hypoalbuminemia promotes increased levels of free (i.e., unbound) arachidonic acid, which may facilitate synthesis of proaggregants, such as thromboxane A2.

Although these changes increase the risk of thrombotic events throughout the vasculature, the renal vein is especially susceptible. One of the main reasons is thought to be fluid loss at the glomerulus, which concentrates postglomerular plasma and thereby increases the risk of thrombus formation.

PRESENTATION AND DIAGNOSIS

RVT may be classified as acute or chronic, depending on the size of the clot and degree of obstruction. A chronic RVT is typically a small clot causing incomplete obstruction. It is often asymptomatic, although in some cases the progressive development of collateral circulation may result in a noticeable varicocele or dilated epigastric vein. In most cases, however, a chronic RVT is not discovered unless the patient has a more acute (i.e., pulmonary) thrombus.

An acute RVT, in contrast, is a large clot causing either complete or near-complete obstruction of renal venous outflow. It presents with symptoms of renal infarction, including nausea/vomiting, flank pain, and gross or microscopic hematuria. In very rare cases, the tense, enlarged kidney may be palpable. If there are bilateral thrombi, acute kidney injury may occur, with a rapid increase in serum creatinine concentration. Acute RVT is an uncommon presentation among patients with nephrotic syndrome and is more characteristic of cases related to hypovolemia or renal trauma.

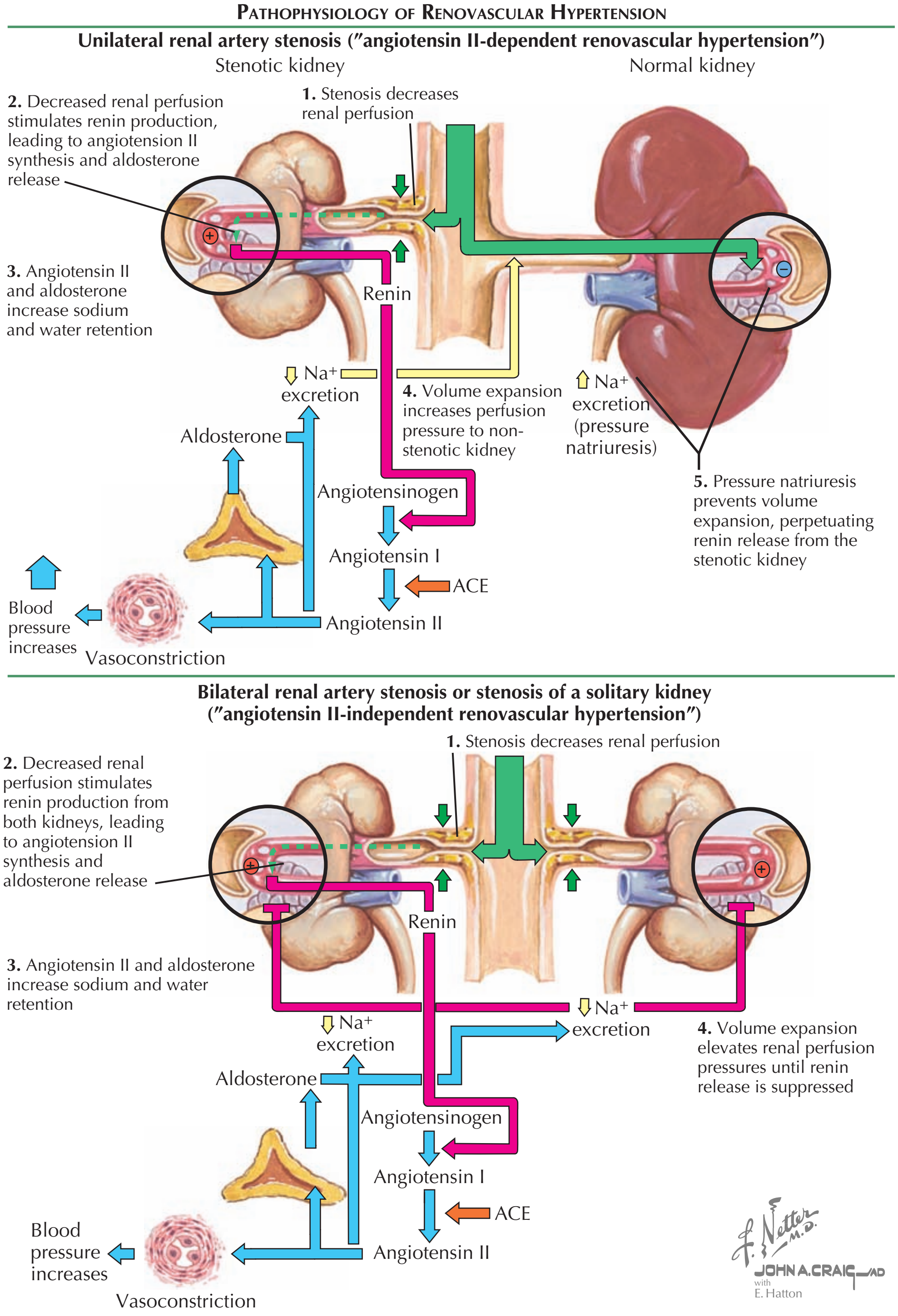
In a patient whose body habitus permits accurate depiction of the renal veins, ultrasound may be used for initial evaluation. A clot may be seen in the vessel lumen, and color Doppler examination may reveal either increased turbulence and flow velocities in partial obstruction, or a lack of flow altogether in complete obstruction. Especially in acute cases, the kidney may appear enlarged and less echogenic than usual because of diffuse edema. The diagnostic utility of ultrasound, however, also depends on the angle of the vein and operator experience.

Spiral computed tomography (CT) with contrast enhancement and magnetic resonance venography (MRV) are typically performed for further evaluation and are highly sensitive modalities. These tests have largely replaced invasive renal venography, which was previously the gold standard. They reveal the thrombus to be a relatively lucent intraluminal defect surrounded by or occluding the flow of contrast-enhanced blood. The vein may be enlarged and, if the thrombus is chronic, renocaval varices may appear. If there is acute ischemia, the kidney appears swollen, with diminished and inhomogeneous enhancement. A tumor, if present, may have visible internal vessels.

TREATMENT

Patients diagnosed with either acute or chronic renal vein thrombosis require anticoagulation treatment. Unfractionated or low molecular weight heparin is appropriate for initial treatment. Although most patients have adequate antithrombin III levels for heparin treatment, the rare patient with extremely low levels may require fresh frozen plasma. Patients should undergo subsequent transition to warfarin, with a target international normalized ratio (INR) of 2.0 to 3.0, and continue on this therapy for as long as the nephrotic syndrome remains. If there are contraindications to anticoagulation, an inferior vena cava filter may be placed. In addition, in the rare case of acute RVT, percutaneous thrombectomy or thrombolysis may be considered. Open surgery should be reserved for those patients with renal failure and bilateral acute thrombosis who cannot be treated with percutaneous techniques.

RENAL ARTERY STENOSIS



PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION

Unilateral renal artery stenosis ("angiotensin II-dependent renovascular hypertension")
Stenotic kidney
Normal kidney
1. Stenosis decreases renal perfusion
2. Decreased renal perfusion stimulates renin production, leading to angiotensin II synthesis and aldosterone release
3. Angiotensin II and aldosterone increase sodium and water retention
Renin
Na+ excretion
4. Volume expansion increases perfusion pressure to non-stenotic kidney
Na+ excretion (pressure natriuresis)
5. Pressure natriuresis prevents volume expansion, perpetuating renin release from the stenotic kidney
Aldosterone
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Blood pressure increases
Vasoconstriction
Bilateral renal artery stenosis or stenosis of a solitary kidney ("angiotensin II-independent renovascular hypertension")
1. Stenosis decreases renal perfusion
2. Decreased renal perfusion stimulates renin production from both kidneys, leading to angiotensin II synthesis and aldosterone release
3. Angiotensin II and aldosterone increase sodium and water retention
Renin
Na+ excretion
Na+ excretion
4. Volume expansion elevates renal perfusion pressures until renin release is suppressed
Aldosterone
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
Blood pressure increases
Vasoconstriction
F. Netter M.D.
JOHN A.CRAIG AD
with E. Hatton

Renal artery stenosis (RAS) is an uncommon but important cause of secondary hypertension. It is unclear what fraction of hypertension is related to this problem; however, it is currently estimated that 1% to 2% of patients with mild to moderate hypertension have clinically significant RAS. Establishing whether the RAS is the primary cause of hypertension in such patients is difficult.

In addition to its effects on blood pressure, RAS can also lead to impaired renal function, a phenomenon known as ischemic nephropathy.

PATHOPHYSIOLOGY

A substantial portion of the aging population has some degree of RAS, which may be discovered as an incidental finding during color Doppler ultrasound or other vascular imaging studies. Indeed, roughly 20% to 45% of the patients who undergo angiography for any indication will be found to have RAS. Once the stenosis occludes more than approximately 50% to 70% of the arterial lumen, a significant drop in pressure distal to the lesion produces a series of pathophysiologic events that lead to a fall in renal blood flow and rise in systemic arterial pressure.

First, reduced perfusion pressure to the affected kidney decreases hydrostatic pressure in the glomeruli and thereby reduces tubular flow rates, triggering release of renin and synthesis of angiotensin II and aldosterone. These hormones increase systemic pressure and promote volume retention, leading to secondary hypertension.

If the contralateral kidney is normal, it will be exposed to these circulating hormones and initially contribute to volume expansion. As its perfusion pressure increases above normal, however, the contralateral kidney will begin to excrete sodium and water. This phenomenon, known as "pressure natriuresis," relies on mechanisms that are incompletely understood. Although autoregulation generally prevents increased perfusion pressure from reaching the glomerular capillaries, it has been hypothesized that increased shear stress in the preglomerular vessels, as well as increased renal interstitial hydrostatic pressure, may activate local natriuretic mechanisms. As a result, the nonstenotic kidney prevents effective volume expansion, and the persistently underperfused stenotic kidney continues to secrete renin. At least in the early stages, the hypertension is thus angiotensin-dependent; however, later in the disease course, renin levels fall as alternate pressor mechanisms, such as endothelin and oxidative stress, are recruited.

If, in contrast, the contralateral kidney is absent or dysfunctional, or if both kidneys are affected by RAS, renin secretion will lead to unopposed expansion of fluid volume. Once there is enough volume to achieve normal perfusion pressure in the stenotic kidney (or kidneys), renin secretion ceases.

During these processes, the affected kidney may itself become dysfunctional, a phenomenon known as "ischemic nephropathy." The kidney as a whole does not become "ischemic" per se because its blood supply generally continues to exceed overall metabolic requirements. Nonetheless, the decline in pressure causes autoregulation to become ineffective, leading to focal areas of tissue injury and ischemia. In addition, the hemodynamic changes lead to altered expression of endothelium-derived substances, such as nitric oxide and endothelin, and promoters of fibrogenic injury, such as transforming growth factor β. As a result, the kidney may exhibit a variable degree of tubulointerstitial fibrosis. If there is bilateral disease, overall filtration may become impaired.

The RAS itself reflects the presence of either atherosclerotic disease, which accounts for approximately 90% of cases, or fibromuscular dysplasia, which accounts for most of the remainder.

Atherosclerosis is a common problem, especially among individuals over 50 years of age. It is associated with risk factors including smoking, diabetes mellitus, and hypercholesterolemia. Because hypertension is also a well-known risk factor for atherosclerosis, many patients with atherosclerotic RAS may also have essential hypertension. Atherosclerosis typically affects the proximal region of the renal artery and the perirenal aorta.

Fibromuscular dysplasia comprises a group of angiopathies that typically occur in women of child-bearing age. Their etiology is unknown. These disorders can lead to fibroplasia in all layers of the arterial wall, but most cases involve the media. A smaller number of cases may feature intimal hyperplasia, which typically leads to dissection and eventual thrombosis. Unlike atherosclerosis, fibromuscular dysplasia typically affects the distal two thirds of the renal arteries.

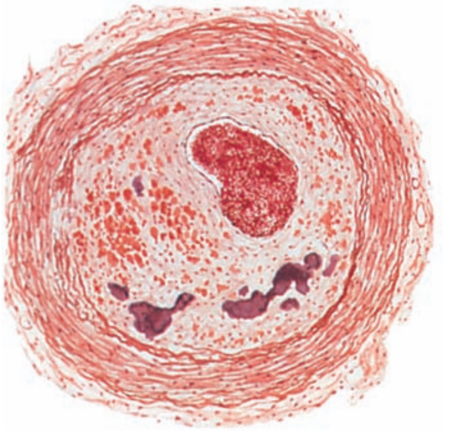
PRESENTATION AND DIAGNOSIS

Few, if any, clinical features can distinguish patents with renovascular hypertension from those with essential

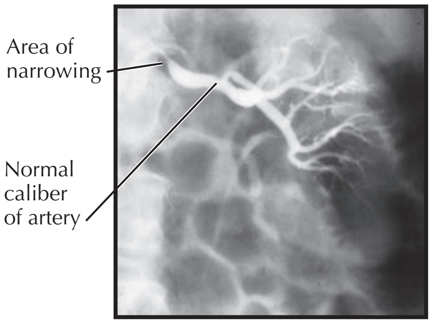
RENAL ARTERY STENOSIS

(Continued)

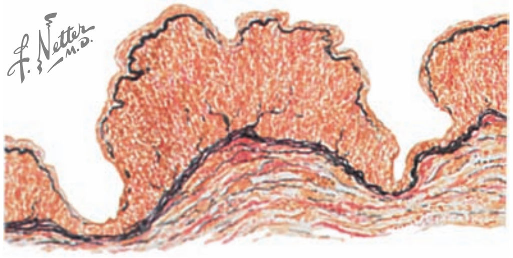
CAUSES OF RENAL ARTERY STENOSIS



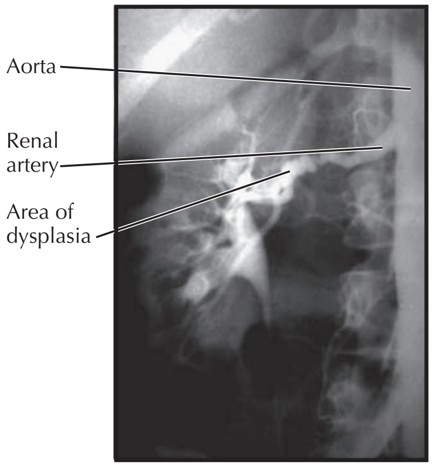
Severe concentric atherosclerosis with lipid deposition and calcification complicated by thrombosis



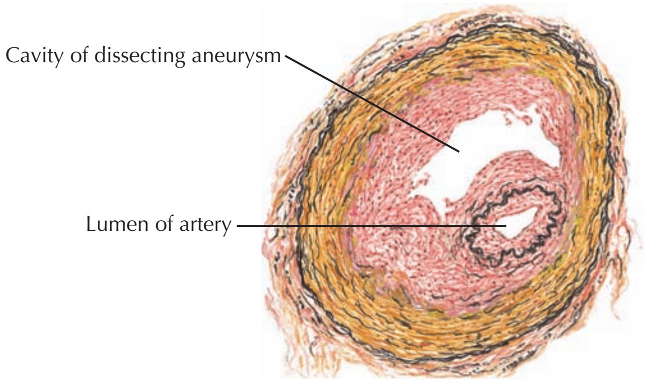
Selective arteriogram demonstrating asymmetrical narrowing of proximal left renal artery by atherosclerotic plaque



Medial fibroplasia (longitudinal section) with variation in mural thickness, chiefly of media, and aneurysmal evaginations



Fibromuscular dysplasia affecting the distal portion of the right renal artery. Alternate stenoses and dilations produce a characteristic beaded appearance



Intimal fibroplasia in branch of renal artery

hypertension. Although some features are suggestive, none is particularly sensitive or specific.

In the clinical history, suggestive features include the onset of hypertension before age 30 or after age 50 (which favor fibromuscular dysplasia or atherosclerosis, respectively); an acute rise in blood pressure in patients with previously well-controlled essential hypertension; refractory hypertension despite multiple treatments; accelerated or malignant hypertension; and the presence of other vascular disease.

On physical examination, an abdominal bruit may be noted. On laboratory studies, suggestive features include hypokalemia (reflecting increased potassium secretion secondary to aldosterone release), an increased BUN : creatinine ratio (reflecting increased proximal tubule reabsorption secondary to angiotensin II release); a significant elevation in serum creatinine concentration after starting an ACE inhibitor or ARB; and a lack of evidence for intrinsic renal disease (e.g., benign urine sediment). On abdominal imaging, one kidney may also appear markedly smaller than the other in the setting of unilateral disease.

If the index of suspicion is high, more specific tests may be performed, but these should be performed mainly if an interventional procedure would be undertaken in the event that RAS were confirmed.

Noninvasive tests include measurement of plasma renin (including after administration of captopril, which removes the negative feedback from angiotensin II), as well as nuclear scanning of renal function after captopril administration. These tests, however, are not highly sensitive or specific in many populations because, for the reasons discussed previously, renin secretion varies widely.

Imaging studies may be performed to directly evaluate the renal vasculature, including Doppler ultrasound (US), computed tomographic angiography (CTA), or magnetic resonance angiography (MRA). US may reveal increased flow velocities across the narrowed vessel, and calculation of the resistive index (which indicates small-vessel disease and parenchymal fibrosis) may indicate the potential benefit of intervention. US, however, is operator-dependent and varies widely between institutions.

CTA and MRA, in contrast, are highly sensitive tests that are widely available; however, these sometimes fail to detect lesions associated with fibromuscular dysplasia, which affect the more distal segments of the renal artery. In addition, these tests require the use of iodinated contrast or gadolinium, which limits their availability to patients with reduced kidney function. Because of its risks and costs, invasive angiography is generally not performed unless an intervention is planned for the same procedure.

For patients with ambiguous degrees of vascular occlusive disease, demonstrating lateralization of renal vein renin levels reliably predicts the role of the affected kidney in sustaining hypertension and the likely effect of revascularization on arterial pressure.

TREATMENT

ACE inhibitors or ARBs should be offered to patients with RAS, either alone or in combination with other antihypertensives, to lower systemic blood pressure. In unilateral disease, the nonstenotic kidney is typically able to compensate for the reduced filtration that these agents cause in the affected kidney. In bilateral disease, however, some patients will experience a clinically significant decline in overall glomerular filtration rate in response to these agents. Thus, in all patients, serum creatinine and potassium concentrations should be measured shortly after these agents are initiated.

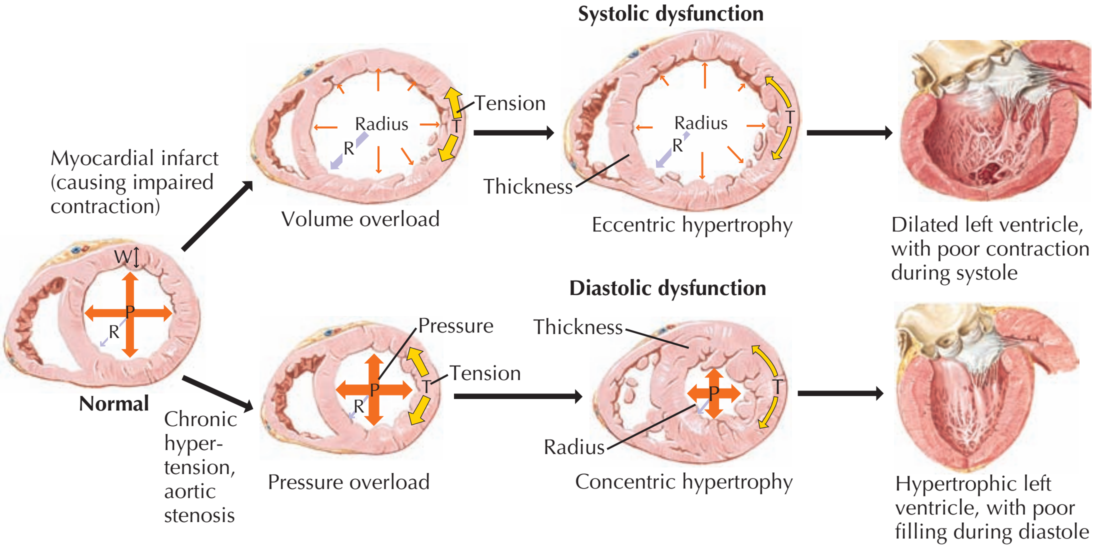
In patients with atherosclerotic disease, measures should be taken to limit the progression of plaque formation, including smoking cessation and administration of statins.

The indications for renal revascularization are controversial, particularly for patients with satisfactory blood pressure control and stable kidney function. In general, interventions should be considered in patients who have drug-resistant or malignant hypertension. In addition, intervention should be considered in patients who have either bilateral stenosis or stenosis to a solitary kidney along with normal or mildly impaired renal function and no evidence of intrinsic renal disease. Although it is difficult to predict which patients with renal dysfunction will benefit the most from revascularization, some evidence suggests that patients with high resistance indices on ultrasound are unlikely to regain much function because they are more likely to have chronic, irreversible renal disease.

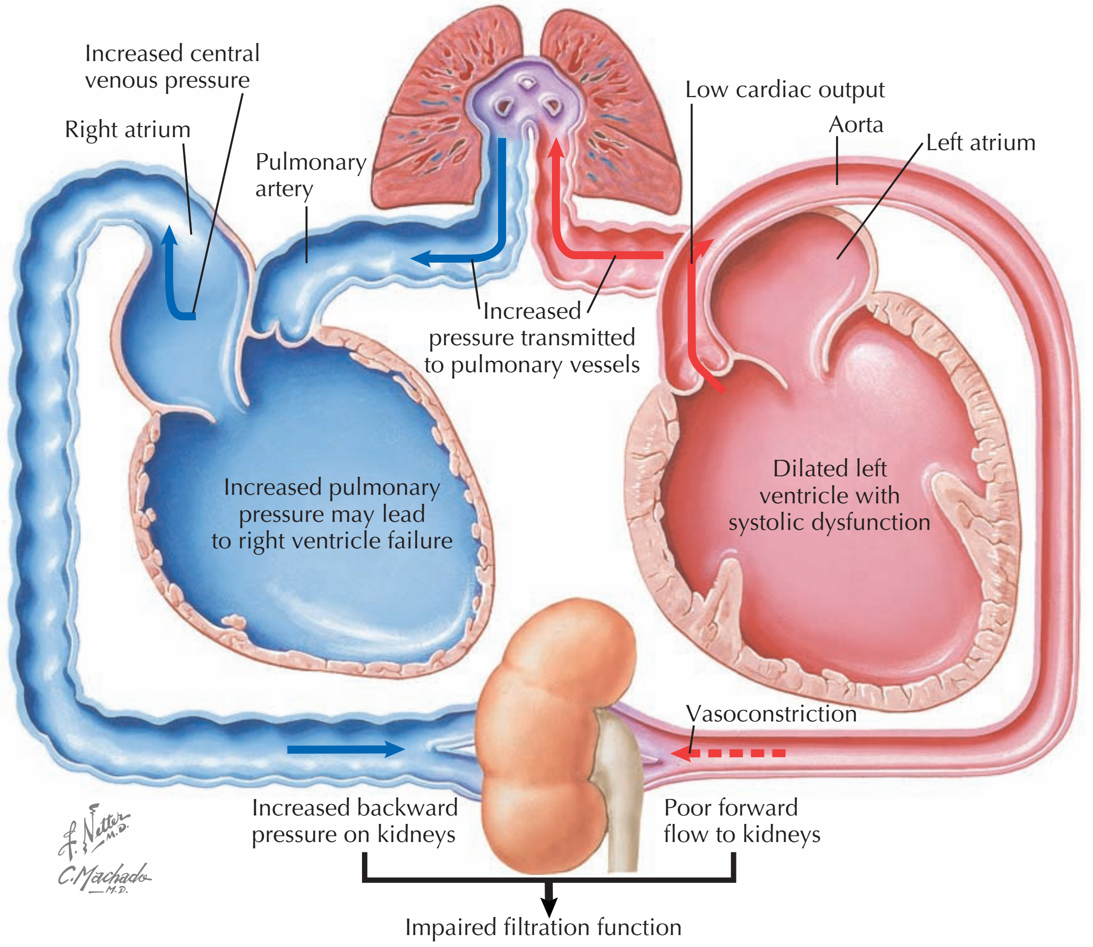
Endovascular repair is generally the preferred method of intervention. It consists of balloon angioplasty and, in patients with atherosclerosis, stent placement. Surgical bypass of the renal artery may be indicated in patients with complex lesions.

TYPES OF LEFT HEART FAILURE AND EFFECTS ON RENAL FUNCTION

Mechanisms of congestive left heart failure


Systolic dysfunction
Myocardial infarct (causing impaired contraction)
W
P
R
Normal
Radius
R
Tension
T
Thickness
Volume overload
Radius
R
T
Eccentric hypertrophy
Dilated left ventricle, with poor contraction during systole
Diastolic dysfunction
Chronic hyper-tension, aortic stenosis
Pressure
Tension
P
T
R
Pressure overload
Thickness
Radius
P
T
Concentric hypertrophy
Hypertrophic left ventricle, with poor filling during diastole

Effects of congestive left heart failure


Increased central venous pressure
Right atrium
Pulmonary artery
Low cardiac output
Aorta
Left atrium
Increased pressure transmitted to pulmonary vessels
Increased pulmonary pressure may lead to right ventricle failure
Dilated left ventricle with systolic dysfunction
Vasoconstriction
Increased backward pressure on kidneys
Poor forward flow to kidneys
Impaired filtration function

CONGESTIVE HEART FAILURE

There is a strong association between congestive heart failure (CHF) and kidney disease, and either one can precipitate the other. The term "cardiorenal syndrome" is often used as an umbrella term to describe the interdependency of the two organs in the disease state.

This section will focus on the prerenal state that may occur in the setting of CHF. For a discussion of the cardiovascular sequelae of chronic kidney disease, refer to the overview of the latter (see Plate 4-66).

PATHOPHYSIOLOGY

Heart failure is defined as the inability of the heart to provide sufficient output to meet perfusion and oxygenation requirements while maintaining normal filling pressures. Insufficient forward flow in the setting of heart failure is sensed by central vascular receptors, and it stimulates the release of norepinephrine, angiotensin II, endothelin, and other cytokines that cause vasoconstriction. These hormones favor perfusion of tissues with high oxygen extraction (brain, heart, skeletal muscle) over tissues with low oxygen extraction (skin, kidneys, splanchnic organs).

In the kidneys, these hormones promote avid reabsorption of salt and water throughout the tubule. In addition, they cause an overall shift in perfusion from short-looped (cortical) to long-looped (juxtamedullary) nephrons, which have a greater sodium reabsorptive capacity. The resulting increase in total volume is intended as an adaptive process, given the perceived arterial underfilling. Ultimately, however, it causes further impairment of cardiac function and worsening of pulmonary and peripheral edema.

In this setting, heart failure may cause a prerenal state because of two distinct but related phenomena. First, the decreased cardiac output ("forward failure") and renal vasoconstriction lead to reduced renal perfusion pressure. If severe enough, the hypoperfusion may overcome normal compensation mechanisms and cause a reduction in glomerular filtration rate. In addition, the chronic increase in venous pressure ("backward failure") behind the failing heart is transmitted to the renal veins, which further impairs renal function. It is not clear how increased renal venous pressure impairs filtration; however, the mechanism likely includes increased levels of sympathetic tone, angiotensin II, and endothelin, all of which cause intrarenal vasoconstriction.

EPIDEMIOLOGY

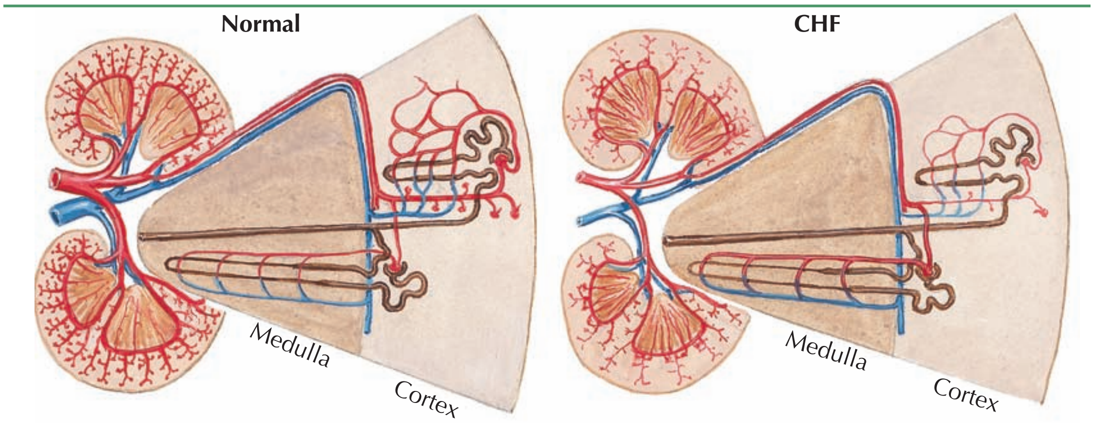
The incidence of chronic kidney disease in the heart failure population has been difficult to estimate, but it likely ranges somewhere between 20% and 67%, with higher incidence associated with older age, diabetes, and hypertension.

In the setting of acute decompensated CHF, both baseline renal dysfunction and worsening renal dysfunction during hospitalization have been identified as significant predictors of hospitalization length, in-hospital mortality, and mortality after discharge.

Large databases, such as the Acute Decompensated Heart Failure National Registry, have suggested that approximately 30% of patients hospitalized with acute decompensated heart failure have concomitant renal insufficiency (based on a report of the first 100,000 patients). A rise in serum creatinine of more than 0.3 mg/dL is associated with a 2.3 day increase in hospitalization length and 67% increased risk of death within 6 months of discharge. The drastic increase in mortality associated with concomitant renal dysfunction is not fully understood but is likely in part due to

Effects of Left Heart Failure on Renal Blood Flow and Tubular Function

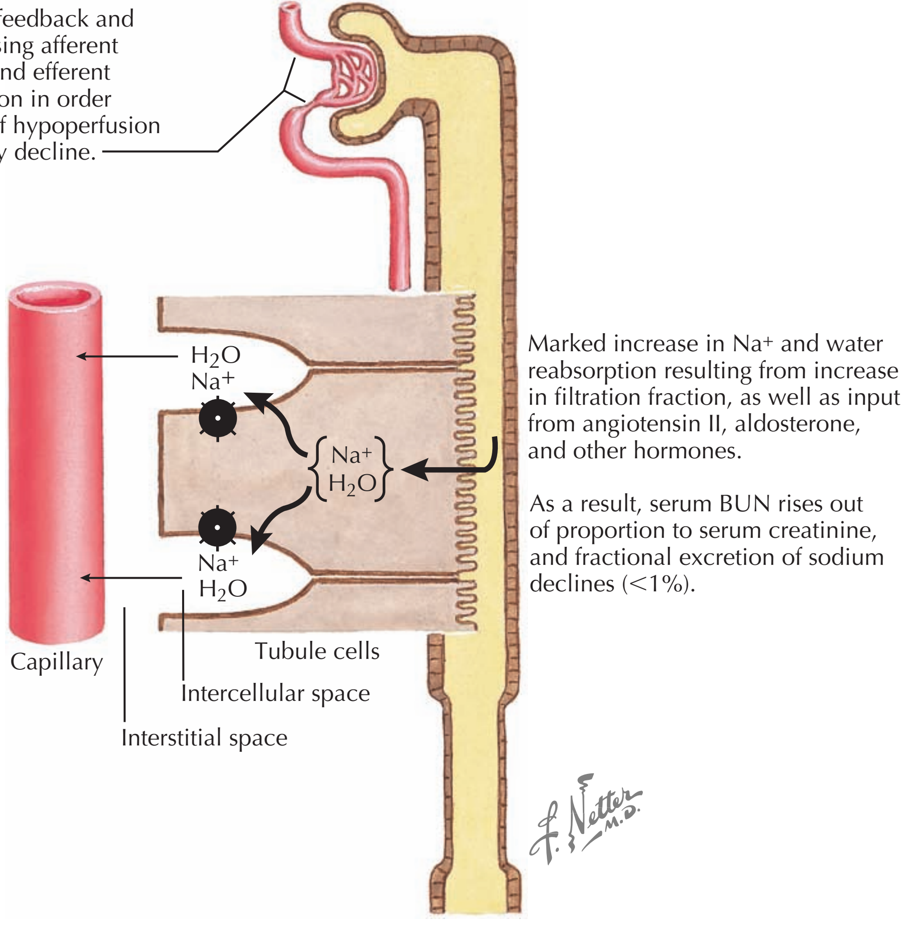
Distribution of renal blood flow in CHF



20% to 25% of cardiac output flows through kidneys: blood flows largely through cortical glomeruli, partially through juxtamedullary glomeruli

<10% of cardiac output flows through kidneys: redistribution of blood flow from cortical to juxtamedullary glomeruli

Tubular function in CHF



Low perfusion pressure activates tubuloglomerular feedback and renin release, causing afferent arteriole dilation and efferent arteriole constriction in order to maintain GFR. If hypoperfusion is severe, GFR may decline.

Marked increase in Na^+ and water reabsorption resulting from increase in filtration fraction, as well as input from angiotensin II, aldosterone, and other hormones.

As a result, serum BUN rises out of proportion to serum creatinine, and fractional excretion of sodium declines (<1%).

CONGESTIVE HEART FAILURE

(Continued)

inflammatory risk factors that are associated with kidney disease and which accelerate cardiovascular risk.

PRESENTATION AND DIAGNOSIS

Patients with CHF typically complain of dyspnea with exertion, orthopnea, and paroxysmal nocturnal dyspnea. Physical examination may reveal stigmata of advanced CHF, including low blood pressure, crackles on lung examination, elevated jugular venous pressure, ascites, and edema.

If an elevation in serum creatinine concentration is noted, prerenal state must be distinguished from causes of intrinsic AKI, such as acute tubular necrosis. In addition to a detailed history, several laboratory findings can help facilitate the distinction. For a detailed discussion, see Plates 4-1 and 4-2.

TREATMENT

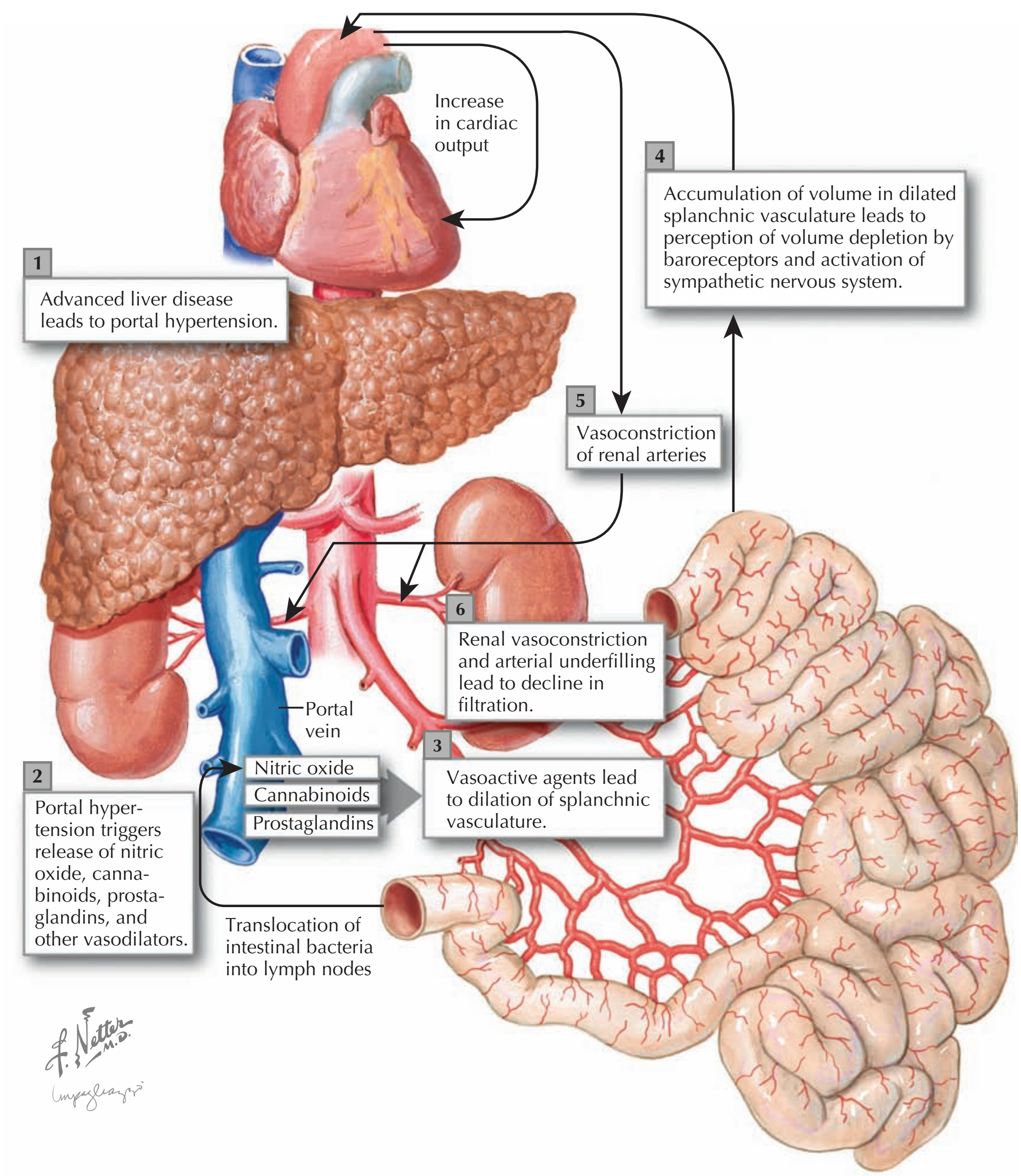
Diuretics, as well as salt and water restriction, are the main treatment for controlling symptoms of volume overload in patients with CHF and prerenal state. In advanced stages of disease, however, they are often unsuccessful in reversing volume overload. Loop diuretics (e.g., furosemide) are highly protein-bound and thus enter the tubular lumen primarily by secretion in the proximal tubule, rather than filtration across the glomerulus. In the setting of decreased renal perfusion, patients may develop diuretic resistance because of decreased diuretic secretion. In such cases, thiazide diuretics (oral metolazone or intravenous chlorothiazide) may need to be added for synergy.

In addition, randomized trials have shown that ACE inhibitor therapy leads to symptomatic improvement, reduced hospitalization, and enhanced survival in patients with systolic heart failure. ACE inhibitors are also widely used in patients with chronic kidney disease because of their cardioprotective and renal protective benefits; however, they must be used with caution in heart failure patients with significant renal insufficiency because of the risk for hyperkalemia and the possibility of worsening GFR.

Renal replacement therapy, in the form of isolated or continuous ultrafiltration for fluid removal, with or without a component of solute clearance (i.e., hemofiltration or hemodialysis), has been increasingly used as a therapeutic tool when diuretics have failed to control symptoms of volume overload.

Heart transplantation is the only potential "cure" for a patient with advanced CHF and kidney dysfunction that is thought to be reversible. Differentiating between prerenal state versus renal parenchymal damage is important when considering heart transplantation alone versus combined heart-kidney transplantation. Unfortunately, based on a recent series of heart transplant candidates, simple laboratory tests at the time of heart transplant evaluation, such as measurement of urine protein excretion and estimated glomerular filtration rate, do not correlate with the degree of fibrosis on renal biopsy. Therefore, in patients with advanced CHF who require transplantation, a renal biopsy may be a crucial step in the preoperative assessment.

PROPOSED PATHOPHYSIOLOGY OF HEPATORENAL SYNDROME


Increase
in cardiac
output
4
Accumulation of volume in dilated splanchnic vasculature leads to perception of volume depletion by baroreceptors and activation of sympathetic nervous system.
1
Advanced liver disease leads to portal hypertension.
5
Vasoconstriction of renal arteries
6
Renal vasoconstriction and arterial underfilling lead to decline in filtration.
Portal
vein
3
Vasoactive agents lead to dilation of splanchnic vasculature.
2
Portal hypertension triggers release of nitric oxide, cannabinoids, prostaglandins, and other vasodilators.
Nitric oxide
Cannabinoids
Prostaglandins
Translocation of
intestinal bacteria
into lymph nodes
F. Netter M.D.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) occurs when there is a decrease in renal perfusion secondary to advanced hepatic disease. Patients may have advanced liver disease due to cirrhosis, alcoholic hepatitis, metastatic cancers, or other causes. HRS is a common complication of liver failure, affecting up to 10% of patients with ascites, and is associated with a significant risk of mortality. As a result, serum creatinine is included in the MELD score (model for end-stage liver disease) used to evaluate patients for possible liver transplantation.

PATHOPHYSIOLOGY

The pathogenesis of HRS appears to be related to vasodilation of the splanchnic circulation, which leads to systemic arterial underfilling. The current evidence indicates that nitric oxide is the primary mediator of splanchnic vasodilation, and several mechanisms have been proposed to trigger its release. First, increased portal venous pressure leads to increased expression of endothelial nitric oxide synthase (eNOS). In addition, as portal hypertension worsens, bacteria traverse from the intestinal lumen into mesenteric lymph nodes, triggering release of inflammatory mediators (such as TNF-α) that further promote eNOS activation. Finally, other vasodilators (including endocannabinoids and prostaglandins), as well as endothelial resistance to vasoconstrictors, are also thought to contribute to the ongoing splanchnic vasodilation.

At first, activation of the sympathetic nervous system and renin-angiotensin-system increases cardiac output and vascular tone to maintain systemic perfusion pressures. As the hepatic disease progresses, however, further compensation becomes impossible. The hepatorenal syndrome thus ensues, in which severe renal vasoconstriction and declining renal perfusion result in a reduced glomerular filtration rate. The consequent retention of sodium and water leads, in turn, to worsening ascites and edema.

In the setting of these processes, several factors can precipitate an acute decompensation in renal function. In patients with advanced liver disease, clinicians must be vigilant about these exacerbating factors:

- Diuretics reduce the intravascular volume, exacerbating the effective volume depletion.
- Occult gastrointestinal bleeding, which may occur because of coagulopathies secondary to advanced liver disease, can worsen volume depletion.
- Large volume paracentesis (especially without the concomitant provision of intravenous albumin, when indicated) can also worsen volume depletion.
- Spontaneous bacterial peritonitis can trigger a dramatic increase in splanchnic inflammatory mediators, promoting further splanchnic vasodilation and worsening effective volume depletion.
- NSAIDs block tubuloglomerular feedback and thus prevent vasodilation of the afferent arteriole in response to poor renal perfusion pressure.

PRESENTATION AND DIAGNOSIS

Patients with HRS often have the typical stigmata of liver disease, which include jaundice, ascites, coagulopathies, and occasionally encephalopathy. Effective intraarterial volume depletion causes tachycardia, low-normal blood pressure, and low jugular venous pressure. The prerenal state leads to oliguria, edema, and worsening ascites.

Suggestive laboratory findings include an elevated serum creatinine concentration, benign urine sediment, and FENa less than 1%. The BUN:Cr ratio may be elevated, indicative of a prerenal state, but BUN must be carefully interpreted since gastrointestinal bleeding and malnutrition can both affect its value. In addition, hyperbilirubinemia may cause granular and epithelial

HEPATORENAL SYNDROME

(Continued)

cell casts, which should not be misinterpreted as evidence of acute tubular necrosis.

Several renal diseases can be associated with specific hepatic diseases; these should be considered and, if possible, ruled out. Examples include IgA nephropathy associated with alcoholic hepatitis; membranous glomerulonephritis associated with hepatitis B; and membranoproliferative glomerulonephritis and cryoglobulinemia associated with hepatitis C.

After a thorough evaluation, the diagnosis of hepatorenal syndrome can be established if the criteria set by the International Club of Ascites are met. Once the diagnosis is confirmed, patients are classified into one of two subtypes based on their rate of progression. Type 1 HRS features rapidly progressive renal failure, defined as a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks. Type 1 HRS usually occurs secondary to a precipitating event, particularly spontaneous bacterial peritonitis or gastrointestinal bleeding, and it has a very poor prognosis. Meanwhile, type 2 HRS features a slower progression of renal failure, manifest as a slowly progressive worsening of serum creatinine to greater than 1.5 mg/dL, and typically occurs without a precipitant.

Note that because of the reduced muscle mass in patients with liver failure, serum creatinine may remain in the normal range during the early stages of renal dysfunction, leading to underdiagnosis. Nonetheless, the serum creatinine concentration steadily increases, although the rate may be as little as 0.1 mg/dL/day, with intermittent periods of stabilization or even slight improvement.

TREATMENT

The treatment of hepatorenal syndrome aims to reverse the underlying circulatory problem until the hepatic disease improves or liver transplantation occurs. Administration of medications that counteract splanchnic vasodilation can help restore renal perfusion, increasing glomerular filtration rate. Multiple pharmacologic therapies have been studied, including vasopressin analogues, midodrine, and octreotide. Transjugular intrahepatic portosystemic shunt (TIPS) is a portal-caval shunt that reduces portal pressure and can improve renal perfusion, but it can also precipitate hepatic encephalopathy and other complications. The use of renal replacement therapy can provide electrolyte stabilization as a bridge to liver transplantation; however, in the absence of planned liver transplantation, dialysis does not significantly improve mortality.

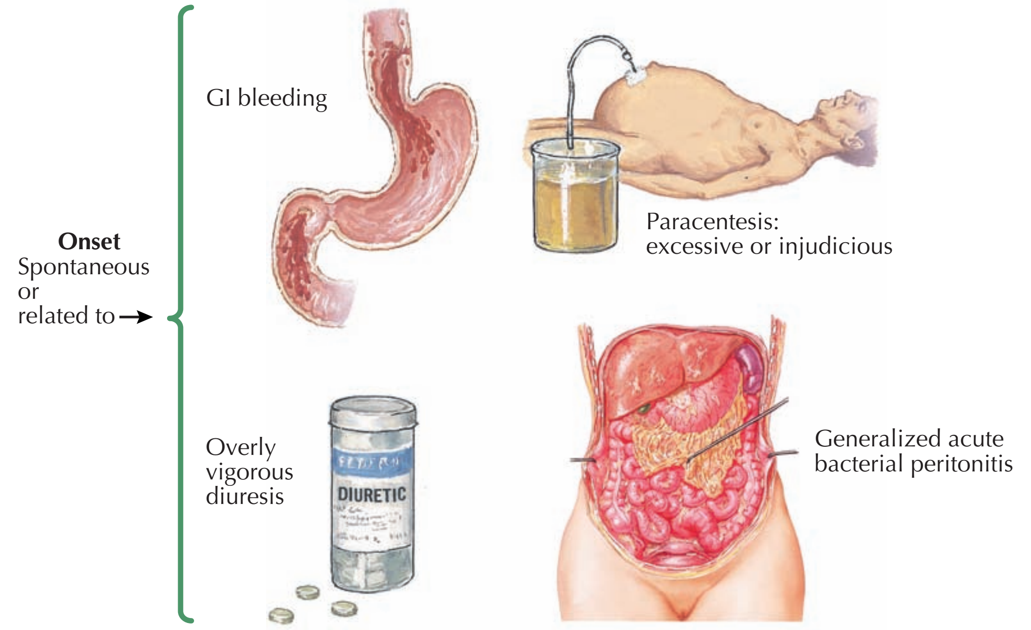
At this time, liver transplantation is the only effective and permanent treatment for hepatorenal syndrome. Unless the renal ischemia is severe enough to cause severe acute tubular necrosis and/or fibrosis, the kidneys remain histologically intact and regain normal function in a majority of cases. Indeed, the kidneys of patients with hepatorenal syndrome are often still suitable for donation to other recipients. Some patients, however, will develop intrinsic renal disease that is advanced enough to warrant a combined liver-kidney transplantation.

PROGNOSIS

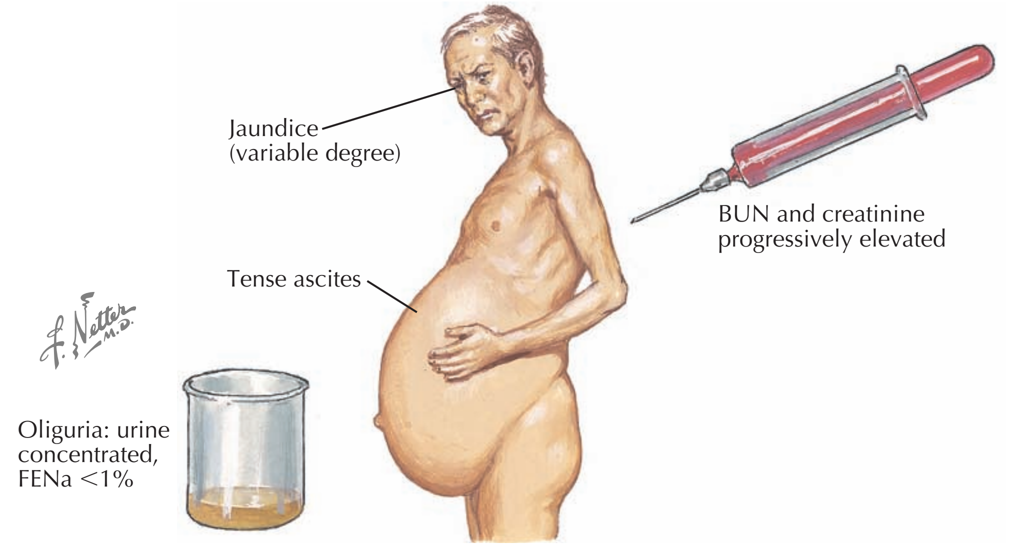
The prognosis is very poor in HRS if treatment is not rapidly provided. Mortality of untreated type I disease, for example, is up to 80% in 2 weeks. Patients with type 2 have a slightly better prognosis, with a median survival of months rather than weeks. Nonetheless, their survival is still shorter than that of a cirrhotic patient with ascites but without renal dysfunction.

SYMPTOMS AND DIAGNOSIS OF HEPATORENAL SYNDROME

Common precipitants of renal dysfunction


GI bleeding
Paracentesis: excessive or injudicious
Onset
Spontaneous or related to →
Overly vigorous diuresis
DIURETIC
Generalized acute bacterial peritonitis

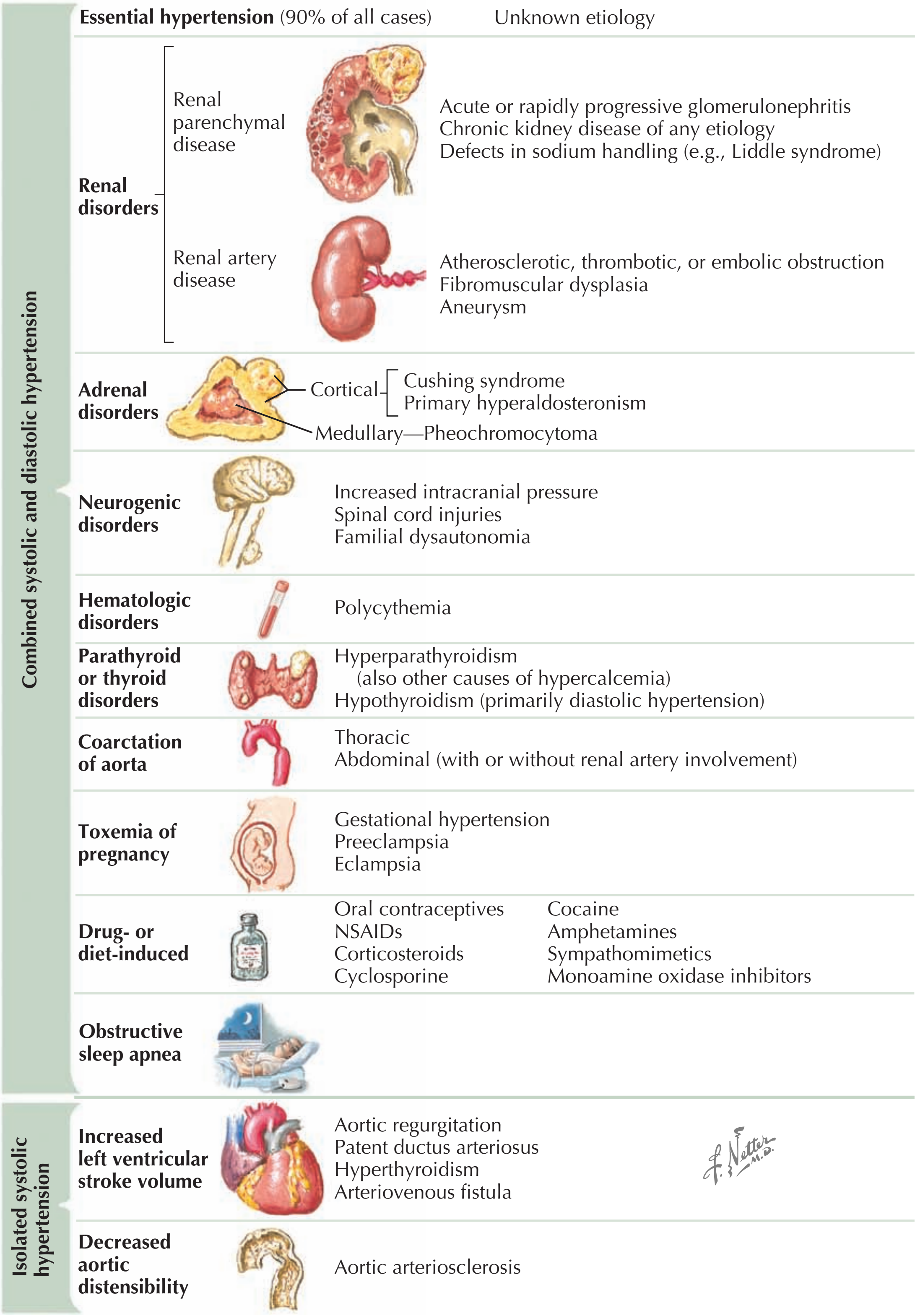
Symptoms of hepatorenal syndrome


Jaundice (variable degree)
BUN and creatinine progressively elevated
Tense ascites
F. Netter M.D.
Oliguria: urine concentrated, FENa <1%

Hepatorenal syndrome: Criteria for diagnosis (International Club of Ascites)

- Presence of cirrhosis and ascites
- Serum creatinine > 1.5 mg/dL
- No improvement in serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended 1 g/kg of body weight per day)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease (i.e., patient does not have proteinuria > 500 mg/day, > 50 RBCs/hpf on urinalysis, or abnormal renal ultrasound)

Major Causes of Hypertension



Essential hypertension (90% of all cases)
Unknown etiology
Combined systolic and diastolic hypertension
Renal disorders
Renal parenchymal disease
Acute or rapidly progressive glomerulonephritis
Chronic kidney disease of any etiology
Defects in sodium handling (e.g., Liddle syndrome)
Renal artery disease
Atherosclerotic, thrombotic, or embolic obstruction
Fibromuscular dysplasia
Aneurysm
Adrenal disorders
Cortical
Cushing syndrome
Primary hyperaldosteronism
Medullary—Pheochromocytoma
Neurogenic disorders
Increased intracranial pressure
Spinal cord injuries
Familial dysautonomia
Hematologic disorders
Polycythemia
Parathyroid or thyroid disorders
Hyperparathyroidism
(also other causes of hypercalcemia)
Hypothyroidism (primarily diastolic hypertension)
Coarctation of aorta
Thoracic
Abdominal (with or without renal artery involvement)
Toxemia of pregnancy
Gestational hypertension
Preeclampsia
Eclampsia
Drug- or diet-induced
Oral contraceptives
NSAIDs
Corticosteroids
Cyclosporine
Cocaine
Amphetamines
Sympathomimetics
Monoamine oxidase inhibitors
Obstructive sleep apnea
Isolated systolic hypertension
Increased left ventricular stroke volume
Aortic regurgitation
Patent ductus arteriosus
Hyperthyroidism
Arteriovenous fistula
F. Netter M.D.
Decreased aortic distensibility
Aortic arteriosclerosis

CHRONIC AND MALIGNANT HYPERTENSION

Chronic hypertension, defined as a baseline blood pressure greater than 140/90 mm Hg, is cited as a leading cause of end-stage renal disease (ESRD), especially among African Americans. The diagnosis of hypertensive kidney disease, or hypertensive nephrosclerosis, is typically made on a clinical basis in those patients who have long-standing hypertension and evidence of renal dysfunction. In most cases, the hypertension is considered essential, meaning known causes (such as renal artery stenosis [see Plate 4-36]) are considered unlikely or have been ruled out.

Although there is firm evidence that uncontrolled hypertension can lead to more rapid progression of existing kidney disease, there is increasing doubt as to whether chronic hypertension is itself a primary cause of kidney disease. Indeed, there is increasing evidence that many individuals diagnosed with hypertensive kidney disease actually have another intrinsic kidney disease, such as focal segmental glomerulosclerosis, that causes hypertension as a secondary effect.

In contrast to the debate regarding chronic hypertension, there is clear evidence that marked and/or sudden increases in blood pressure, known as malignant or accelerated hypertension, can cause renal failure, as discussed in detail at the end of this section.

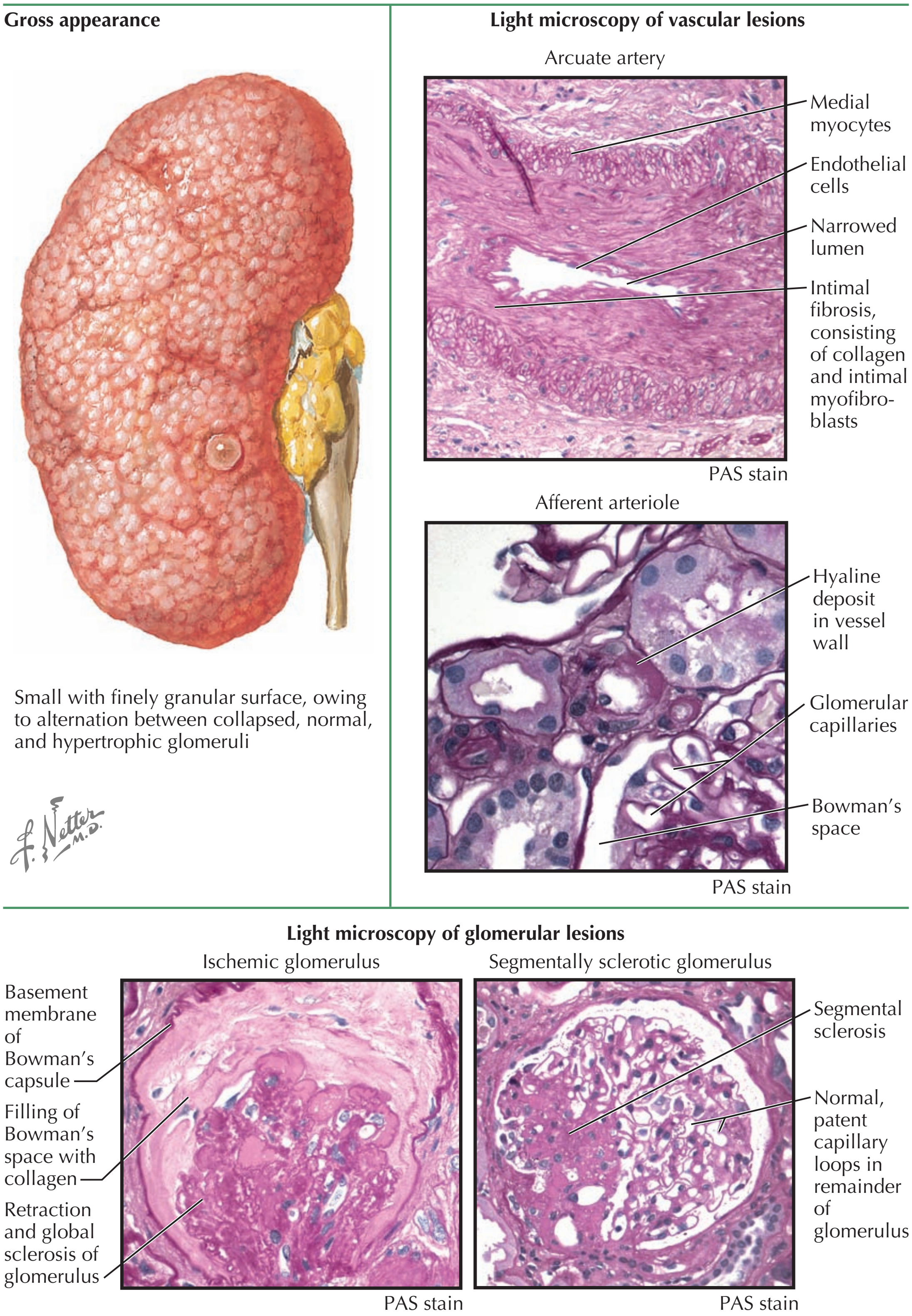
Chronic Hypertension. Chronic elevations in blood pressure have been associated with numerous microvascular changes in multiple organ systems. In the kidney, these changes are prominent in both the preglomerular and glomerular vasculature.

The arcuate and interlobular arteries appear narrowed secondary to fibroplasia of the intima layer, which results from increased deposition of collagen and elastin, as well as migration of myofibroblasts from the media layer. The afferent arterioles, meanwhile, exhibit a lesion known as hyalinosis, which results from insudation of plasma proteins into the vessel wall, where they accumulate as glassy, acellular deposits.

The glomerular capillaries may exhibit several different patterns of involvement. Some tufts appear normal, whereas others appear either segmentally or globally sclerotic. The pattern of global sclerosis may be further characterized as “obsolescence” or “solidification.” In obsolescence, there is wrinkling of the glomerular basement membrane followed by collapse of the entire glomerular tuft toward the vascular pole. The collapsed tuft becomes sclerotic, whereas the enlarged Bowman space is filled in with collagenous material. Meanwhile, in solidification, the glomerular tuft undergoes hypertrophy and then becomes globally sclerotic without collapse.

Even though hypertension is known to be associated with these histopathologic changes, an ongoing question has been whether mild to moderate hypertension

RENAL HISTOPATHOLOGY OF CHRONIC HYPERTENSION


Gross appearance
Small with finely granular surface, owing to alternation between collapsed, normal, and hypertrophic glomeruli
Light microscopy of vascular lesions
Arcuate artery
Medial myocytes
Endothelial cells
Narrowed lumen
Intimal fibrosis, consisting of collagen and intimal myofibroblasts
PAS stain
Afferent arteriole
Hyaline deposit in vessel wall
Glomerular capillaries
Bowman's space
PAS stain
Light microscopy of glomerular lesions
Ischemic glomerulus
Segmentally sclerotic glomerulus
Basement membrane of Bowman's capsule
Filling of Bowman's space with collagen
Retraction and global sclerosis of glomerulus
PAS stain
Segmental sclerosis
Normal, patent capillary loops in remainder of glomerulus
PAS stain

CHRONIC AND MALIGNANT HYPERTENSION *(Continued)*

induces a degree of glomerulosclerosis that results in a clinically significant loss of renal function.

Recent evidence suggests that the severity of the glomerular abnormalities seen in the kidneys do not correlate well with the degree of hypertension or the severity of the preglomerular disease. Moreover, it has been noted that in biopsies of patients with the clinical diagnosis of hypertensive kidney disease, "solidified" glomeruli are more common in African Americans compared with Caucasians, and that they are associated with the presence of segmentally sclerotic glomeruli. In contrast, both groups exhibit a comparable number of obsolescent glomeruli.

These findings raise the possibility that hypertension may be occurring in concert with, or as the result of, a primary glomerular disease, especially in African Americans. Indeed, there is emerging evidence that in many African Americans who receive the diagnosis of "hypertensive kidney disease," hypertension is actually the result of a primary renal disease, rather than its cause.

Recent analysis of the *APOL1* gene, which encodes apolipoprotein L1, has lent further support to this claim. In large groups of African Americans, the presence of two variant *APOL1* alleles was associated with a substantial increase in the risk of biopsy-proven focal segmental glomerulosclerosis and the clinical diagnosis of hypertensive kidney disease. Although the role of apolipoprotein L1 in the kidney is not known, these data suggest that many patients with hypertensive kidney disease actually have focal segmental glomerulosclerosis. Interestingly, the same *APOL1* variant that causes renal disease has also been shown to protect against infection with *Trypanosoma* parasites, which would explain its wide distribution throughout part of the African population.

Thus it appears possible that certain *APOL1* alleles confer a survival advantage to heterozygotes but increase the risk of renal disease among homozygotes. This situation would be akin to the wide distribution of certain hemoglobin mutations that confer protection from malarial parasites to heterozygotes but cause sickle cell disease among homozygotes.

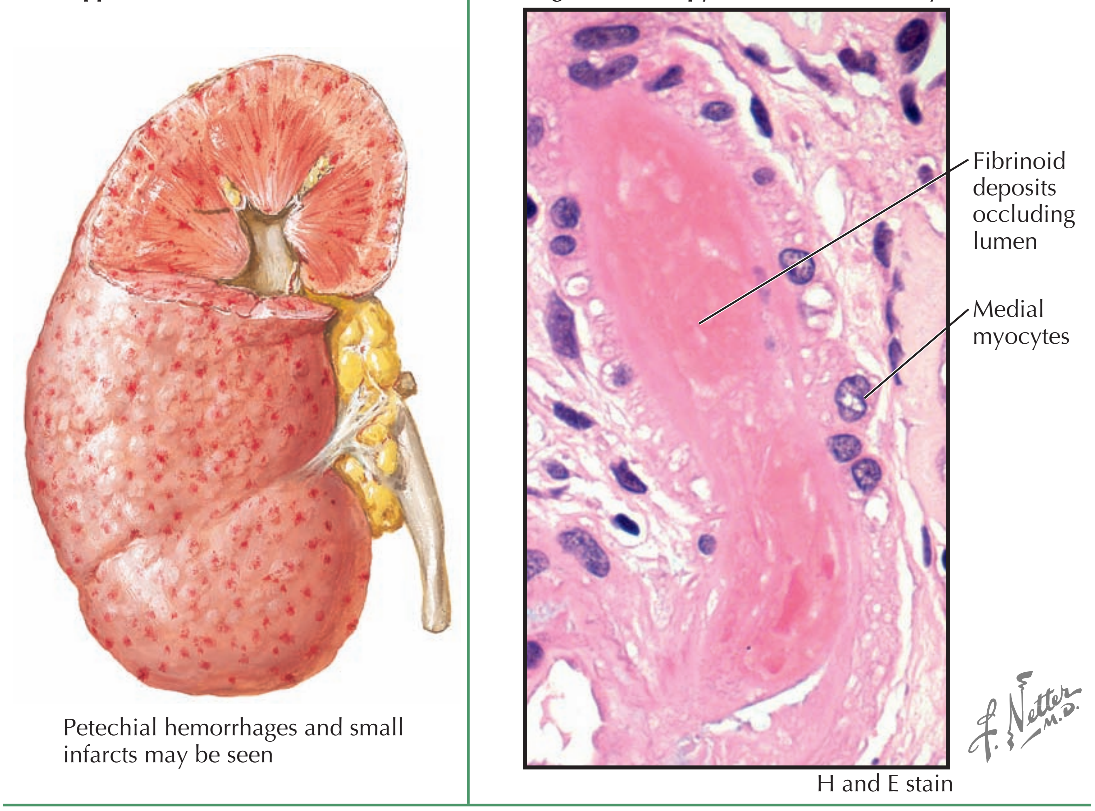
Although these findings do not eliminate the possibility that hypertension is a primary cause of renal disease, they do suggest that it could account for a smaller number of ESRD cases than currently estimated.

Numerous studies have shown that treating hypertension can slow the progression of chronic kidney disease. ACE inhibitors and ARBs exert an additional benefit by reducing proteinuria, which further retards progressive glomerulosclerosis and tubular injury.

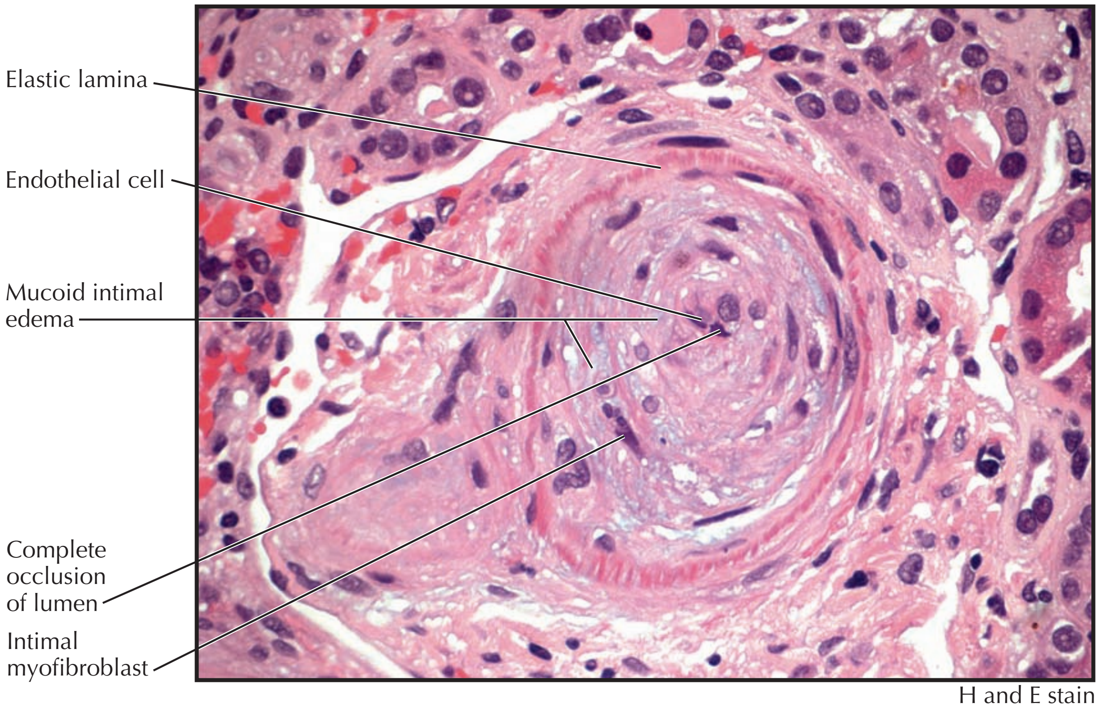
Importantly, however, the African American Study of Kidney Disease and Hypertension Trial (AASK) demonstrated that in patients with hypertension and renal insufficiency, intensive blood pressure control (target MAP of 92 mm Hg) offers no additional benefit over standard control (target MAP of 102 to 107 mm Hg).

RENAL HISTOPATHOLOGY OF MALIGNANT HYPERTENSION

Gross appearance **Light microscopy of interlobular artery**


Petechial hemorrhages and small infarcts may be seen
Fibrinoid deposits occluding lumen
Medial myocytes
F. Netter M.D.
H and E stain

Light microscopy of afferent arteriole



CHRONIC AND MALIGNANT HYPERTENSION *(Continued)*

Malignant Hypertension. Although the connection between chronic hypertension and renal disease remains controversial, there is less ambiguity concerning the effects of severe elevations in blood pressure, which can cause the rapid development of microvascular disease. Such disease may manifest as neurologic changes (headache, seizures, coma), ocular changes (retinal hemorrhage or exudates, papilledema), and renal disease (acute kidney injury, hematuria, proteinuria).

Although there is no strict definition of malignant hypertension, it is generally considered to occur when diastolic pressure exceeds 110 to 120 mm Hg and there is evidence of associated end-organ damage that includes papilledema. If papilledema is absent but other end-organ damage is seen, "accelerated hypertension" is the preferred term. If there is no evidence of end-organ damage despite a very elevated pressure, "hypertensive urgency" is the preferred term.

In untreated malignant hypertension, the kidney grossly shows subcapsular and cortical hemorrhages, sometimes accompanied by small infarcts. At a microscopic level, the major vascular lesion of afferent arterioles is known as "fibrinoid necrosis," in which an acellular, eosinophilic mixture of material that stains like fibrin ("fibrinoid") is deposited into the intima and media. These deposits appear granular, in contrast to the glassy appearance of hyaline deposits. Hemorrhage, thrombosis, and mesangiolysis are often seen. These changes may extend into the glomeruli, usually in a segmental pattern. In the interlobular arterioles, there is often concentric thickening of the intima with mucoid matrix and myointimal cells, which may assume an "onion skin" appearance and occlude the lumen if advanced.

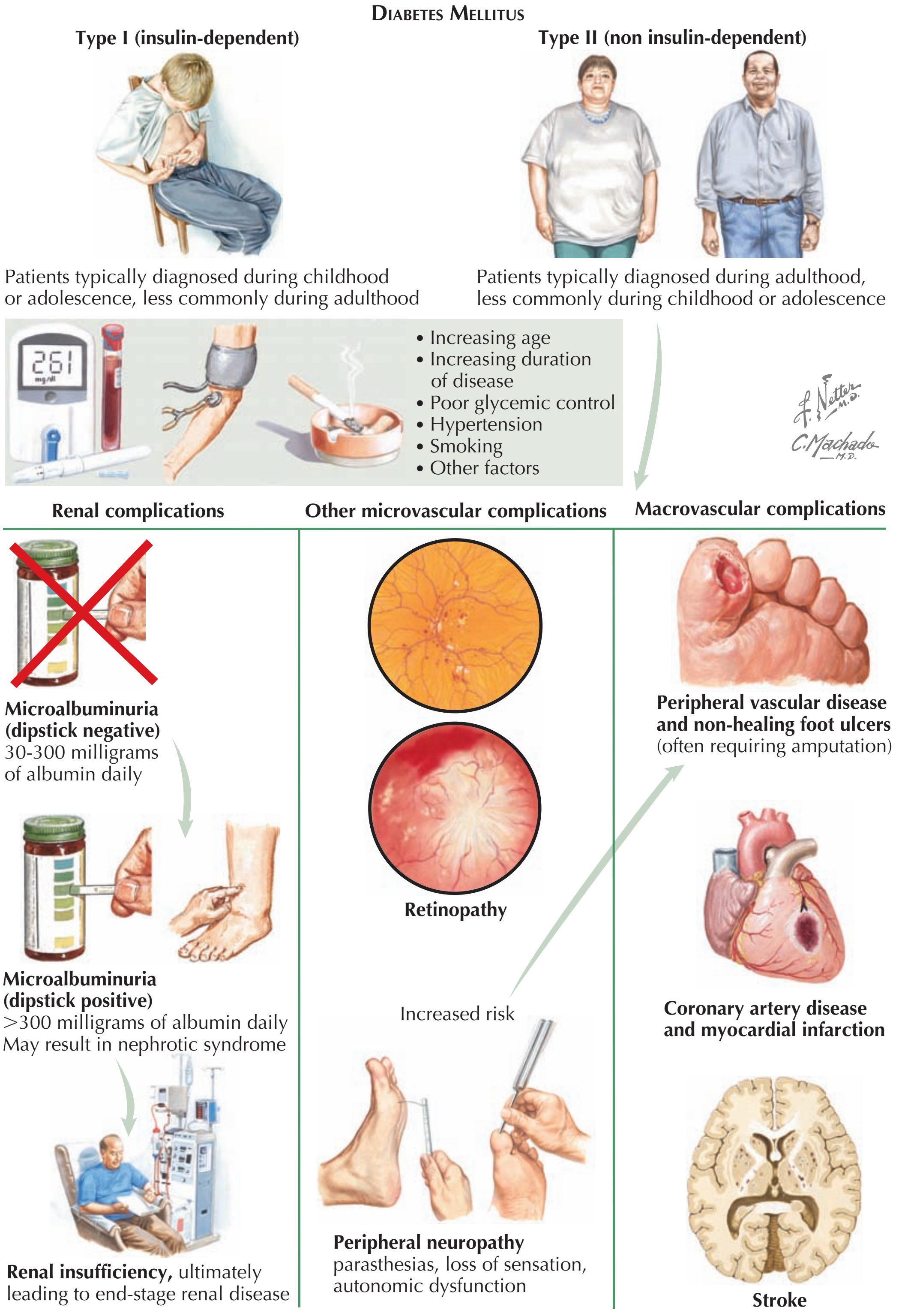
Malignant or accelerated hypertension is a life-threatening emergency, and careful lowering of blood pressure (by no more than 25% of the presenting value) should occur over the course of several hours to prevent organ ischemia from impaired autoregulation. Although fibrinoid necrosis heals with improved blood pressure control, the interlobular arteries may remain narrow, producing glomerular ischemia and collapse.

SUMMARY

Based on the above, patients with hypertension and renal disease can be divided into several groups: those with true "essential hypertension" that may result in renal disease; those with a primary renal disease that causes secondary hypertension but is mislabeled as "hypertensive kidney disease"; and those with malignant hypertension in whom renal failure presents acutely.

No matter the cause of the renal disease, it is clear that uncontrolled hypertension leads to progression of renal failure and should thus be treated aggressively. The optimal blood pressure targets, however, remain unknown.

DIABETIC NEPHROPATHY


Diabetes Mellitus
Type I (insulin-dependent)
Type II (non insulin-dependent)
Patients typically diagnosed during childhood or adolescence, less commonly during adulthood
Patients typically diagnosed during adulthood, less commonly during childhood or adolescence
261
mg/dl
• Increasing age
• Increasing duration of disease
• Poor glycemic control
• Hypertension
• Smoking
• Other factors
F. Netter M.D.
C. Machado M.D.
Renal complications
Other microvascular complications
Macrovascular complications
Microalbuminuria (dipstick negative)
30-300 milligrams of albumin daily
Microalbuminuria (dipstick positive)
>300 milligrams of albumin daily
May result in nephrotic syndrome
Renal insufficiency, ultimately leading to end-stage renal disease
Retinopathy
Increased risk
Peripheral neuropathy
parasthesias, loss of sensation, autonomic dysfunction
Peripheral vascular disease and non-healing foot ulcers
(often requiring amputation)
Coronary artery disease and myocardial infarction
Stroke

Diabetic nephropathy (DN) reflects renal injury in response to chronic long-standing hyperglycemia. It may occur in patients with type I or II diabetes mellitus, and it manifests as progressive albuminuria followed by a decline in the glomerular filtration rate (GFR).

Recent data from the Centers for Disease Control and Prevention estimate that 23.6 million individuals in the United States, or roughly 7.8% of the population, suffer from diabetes mellitus. Because of this rising epidemic, DN is now the leading cause of chronic kidney disease and end stage renal disease (ESRD) in the United States and other countries (both developed and developing).

Among those with type 1 diabetes, the incidence of overt nephropathy (defined as dipstick-positive proteinuria) has declined over recent years, from approximately 30% to 10% at 25 years. Among those with type 2 diabetes, approximately 12% develop overt nephropathy over the same timeframe.

The risk of nephropathy increases with patient age, duration of diabetic disease, hypertension, and poorer glycemic control. Genetic factors also play an important role, insofar as a patient with diabetes mellitus is more likely to develop nephropathy if a sibling or parent has this complication as well. In addition, blacks and certain minority populations (such as Pima Indians) are more likely to develop DN than Caucasians.

PATHOPHYSIOLOGY

The sequence of events that leads to DN is largely unknown. Proposed mechanisms include hyperglycemia-induced hyperfiltration, accumulation of advanced glycation end products, and activation of pro-inflammatory/profibrotic pathways.

An increase in the glomerular filtration rate is the earliest demonstrable abnormality, reflecting afferent arteriolar vasodilation and efferent arteriolar vasoconstriction. The exact link between hyperglycemia and hyperfiltration, however, is not fully understood and probably reflects multiple mechanisms, including abnormalities in tubuloglomerular feedback induced by increased proximal reabsorption of glucose and sodium, effects of advanced glycation end products, and changes in hormonal input (such as from the renin-angiotensin axis). In the long term, increased intraglomerular pressure can lead to glomerulosclerosis. Systemic hypertension can accelerate this process by further increasing intraglomerular pressure.

Meanwhile, hyperglycemia causes increased production of mesangial matrix proteins, leading to mesangial expansion. Angiotensin II and transforming growth factor-β (TGF-β) are important factors in this process, and variations in the genes encoding angiotensin II and its receptors have been found to account for some of the inherited risk for nephropathy. It appears that hyperglycemia stimulates angiotensin II synthesis, which in turn stimulates TGF-β secretion. TGF-β then increases the synthesis and decreases the degradation of matrix proteins, leading to their accumulation. Another hormone known to be involved in this process is vascular endothelial growth factor (VEGF). In animal models of diabetic nephropathy, blockade of TGF-β and VEGF has been shown to have beneficial effects.

Advanced glycation end products (AGEs) also play an important role in promoting mesangial matrix accumulation. These compounds are formed nonenzymatically when proteins are exposed to glucose. They then cross link with normal matrix proteins, such as collagen, and render them resistant to proteolysis. Binding of AGEs to a specific receptor (RAGE) triggers production of reactive oxygen species and subsequent inflammation.

In type 1 diabetes, the pathologic changes to the glomerulus occur in a somewhat predictable sequence, with hypertrophy of the glomeruli and thickening of the basement membrane seen early in the disease course. Expansion of the mesangium then follows and leads to the clinical manifestation of proteinuria. As the disease progresses, there is progressive glomerular damage and increasing amounts of albuminuria, with eventual reduction of the GFR and, ultimately, ESRD.

In type 2 diabetes, these events may be temporally compressed, with impaired renal function appearing as an early manifestation. To some extent this difference may reflect the fact that diagnosis often does not occur until later in the disease course; however, it may also reflect increased patient age in this population and the frequent presence of comorbid hypertension.

PRESENTATION AND DIAGNOSIS

The earliest clinical manifestation of diabetic nephropathy is known as microalbuminuria, defined as 30 to 300 mg of albumin per gram of creatinine in a spot

DIABETIC NEPHROPATHY
(Continued)

urine sample, a quantity of protein that cannot reliably be detected on a urine dipstick. As the disease progresses, macroalbuminuria ensues (>300 mg/g of creatinine in a spot sample), which can be detected on a dipstick and is a marker of overt nephropathy. In some cases, proteinuria may be severe enough to cause the full nephrotic syndrome. The final stages of DN are characterized by a progressive decline in renal function, which can lead to ESRD.

To assess for the presence and degree of proteinuria, all patients with known diabetes mellitus should be evaluated on an annual basis with a quantitive spot urine albumin to creatinine ratio. Such testing should begin 5 years from diagnosis in patients with type 1 diabetes, and at the time of diagnosis in patients with type 2 diabetes. The screening should also include a serum creatinine concentration to evaluate for renal insufficiency and, in patients with overt nephropathy, measurement of serum albumin and lipid concentrations. Monitoring blood pressure is also essential.

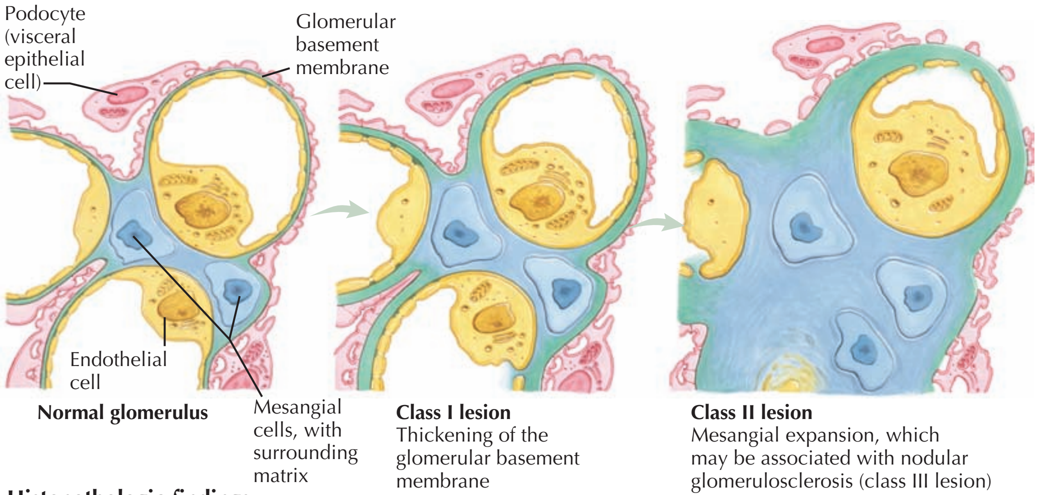
In patients with overt nephropathy, other renal diseases should always be ruled out before diabetes is assumed to be the cause. A renal ultrasound should be performed as part of the workup. Although most renal diseases cause the kidneys to appear shrunken, DN causes them to appear normal-sized or even enlarged. (This finding is not specific, however, because a small number of other diseases such as amyloidosis, also cause enlarged kidneys.)

Renal biopsy is not routinely indicated, but it may be performed if another diagnosis is suspected on clinical or serologic grounds, or if the rate of progression is atypical. For example, a biopsy would be indicated in a patient with an active, cellular urine sediment or a rapid decline in filtration function over the course of weeks or months. Conversely, a diabetic patient with retinopathy, long-standing proteinuria, a bland urine sediment, and a slow decline in renal function can be reasonably assumed to have diabetic nephropathy without a biopsy-proven diagnosis.

Upon biopsy, the pathologic lesion of DN may be classified into one of four classes. Class I features isolated thickening of the glomerular basement membrane; class II features mesangial expansion; class III (also known as nodular glomerulosclerosis or the "Kimmelstiel-Wilson" lesion) features intercapillary nodules resulting from severe mesangial expansion, with compression of adjacent capillary lumina; and class IV features advanced glomerulosclerosis (> 50% of glomeruli have global sclerosis). The correlation between clinical and pathologic findings is often weak, however, and patients with minimal clinical manifestations may undergo biopsies that reveal established diabetic lesions, or vice versa.

DIABETIC NEPHROPATHY

Schematic of glomerular changes

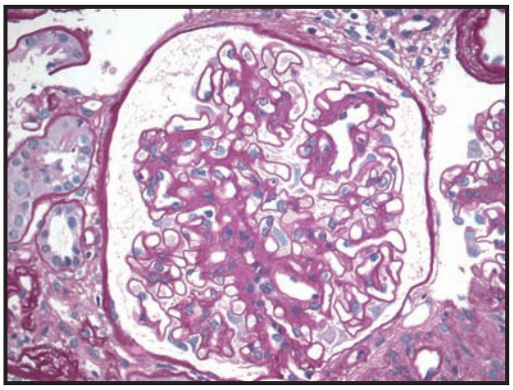

Podocyte (visceral epithelial cell)
Glomerular basement membrane
Endothelial cell
Mesangial cells, with surrounding matrix

Normal glomerulus

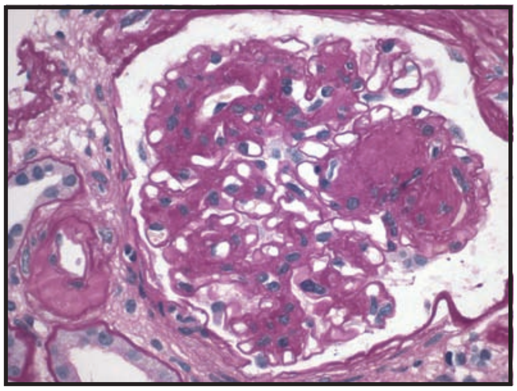
Class I lesion
Thickening of the glomerular basement membrane

Class II lesion
Mesangial expansion, which may be associated with nodular glomerulosclerosis (class III lesion)

Histopathologic findings



Light microscopy of a class II lesion, with diffuse mesangial expansion (PAS stain, 400×)



Light microscopy of a class III lesion, with nodular glomerulosclerosis (PAS stain, 400×)

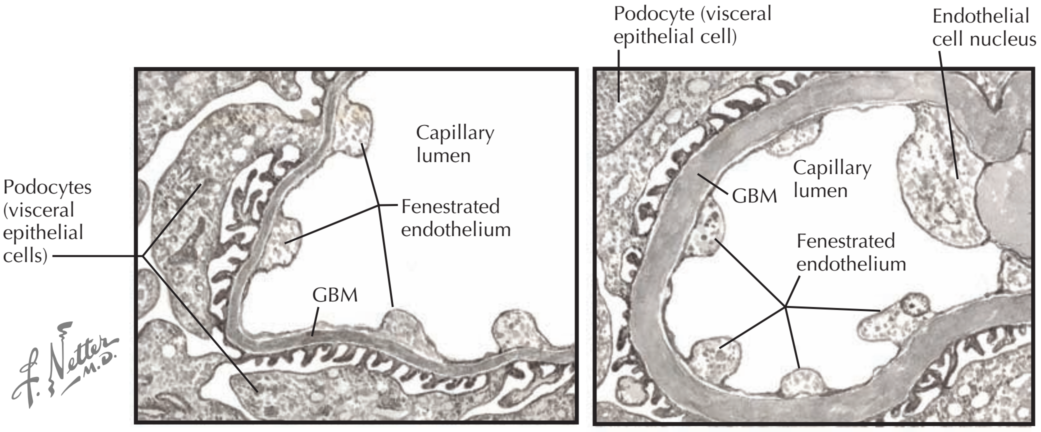


Illustration of electron microscopy of a normal glomerular capillary wall (left), and one affected by diabetic nephropathy. Note significant thickening of the glomerular basement membrane (GBM).

TREATMENT

DN is both prevented and treated by rigorously controlling serum glucose concentrations (goal hemoglobin A_{1C} <7.0) and lowering blood pressure. In the United Kingdom Prospective Diabetes Study, for example, each 10 mm Hg reduction in systolic pressure was associated with a 12% reduction in the risk for diabetic complications, with the lowest risk occurring in patients with a systolic blood pressure under 120 mm Hg.

ACE inhibitors and angiotensin receptor blockers (ARBs) are the preferred antihypertensive agents because they also reduce proteinuria and slow the inflammatory processes that drive further renal dysfunction. They should be offered to all diabetics with hypertension, as well as to all normotensive diabetics with microalbuminuria or macroalbuminuria. Available evidence indicates that these agents may also be effective for delaying the onset of microalbuminuria in patients with no albuminuria.

It is unclear if dietary protein restriction has any role in retarding progression of renal insufficiency. Renal replacement therapy, including dialysis or renal transplantation, is indicated once patients approach ESRD.

PROGNOSIS

A large study of type 2 diabetics found that the annual risk of progression from no albuminuria to microalbuminuria was 2.0%, from microalbuminuria to macroalbuminuria was 2.8%, and from macroalbuminuria to impaired filtration function was 2.3%. Overall, at 10 years after diagnosis, 25% had microalbuminuria or worse, 5% had macroalbuminuria or worse, and 1% had elevated plasma creatinine or were undergoing renal replacement therapy.

AMYLOIDOSIS

Amyloidosis is a multi-system disease in which amyloid protein fibrils deposit and accumulate in various organs, where they cause progressive dysfunction. A wide range of signs and symptoms may be seen depending on the specific organ systems involved.

PATHOPHYSIOLOGY

Amyloid fibrils are rigid, nonbranching, linear fibrils that are 8 to 10 nm wide. They are composed of normally soluble proteins that become misfolded, resulting in structural abnormalities that promote aggregation. Several factors can lead to protein misfolding and fibril formation, such as aging (i.e., transthyretin in senile amyloidosis); elevated serum concentrations (i.e., β_2 microglobulin in dialysis-related amyloidosis); and inherited mutations (i.e., hereditary amyloidosis). Over 20 different proteins have been identified to have amyloidogenic potential. The amyloid fibril structure is the same irrespective of the precursor protein.

In addition to the misfolded proteins, all amyloid fibrils contain a glycoprotein called serum amyloid P component (SAP), which renders them resistant to proteolysis. In addition, fibrils contain glycosaminoglycans, such as heparan sulfate, that play an important role in fibril assembly and the binding of fibrils to target tissues.

It is not entirely clear how deposition of amyloid fibers leads to organ dysfunction. It appears probable, however, that fibril accumulation disrupts normal tissue architecture, and that protofibrils (intermediate fibril structures) cause oxidative stress that triggers apoptosis.

The particular organ distribution of amyloid fibrils appears to depend on poorly understood features of the precursor protein. The amyloid fibrils most often associated with renal disease are formed either by immunoglobulin light chains (AL amyloidosis) or serum amyloid A (AA amyloidosis).

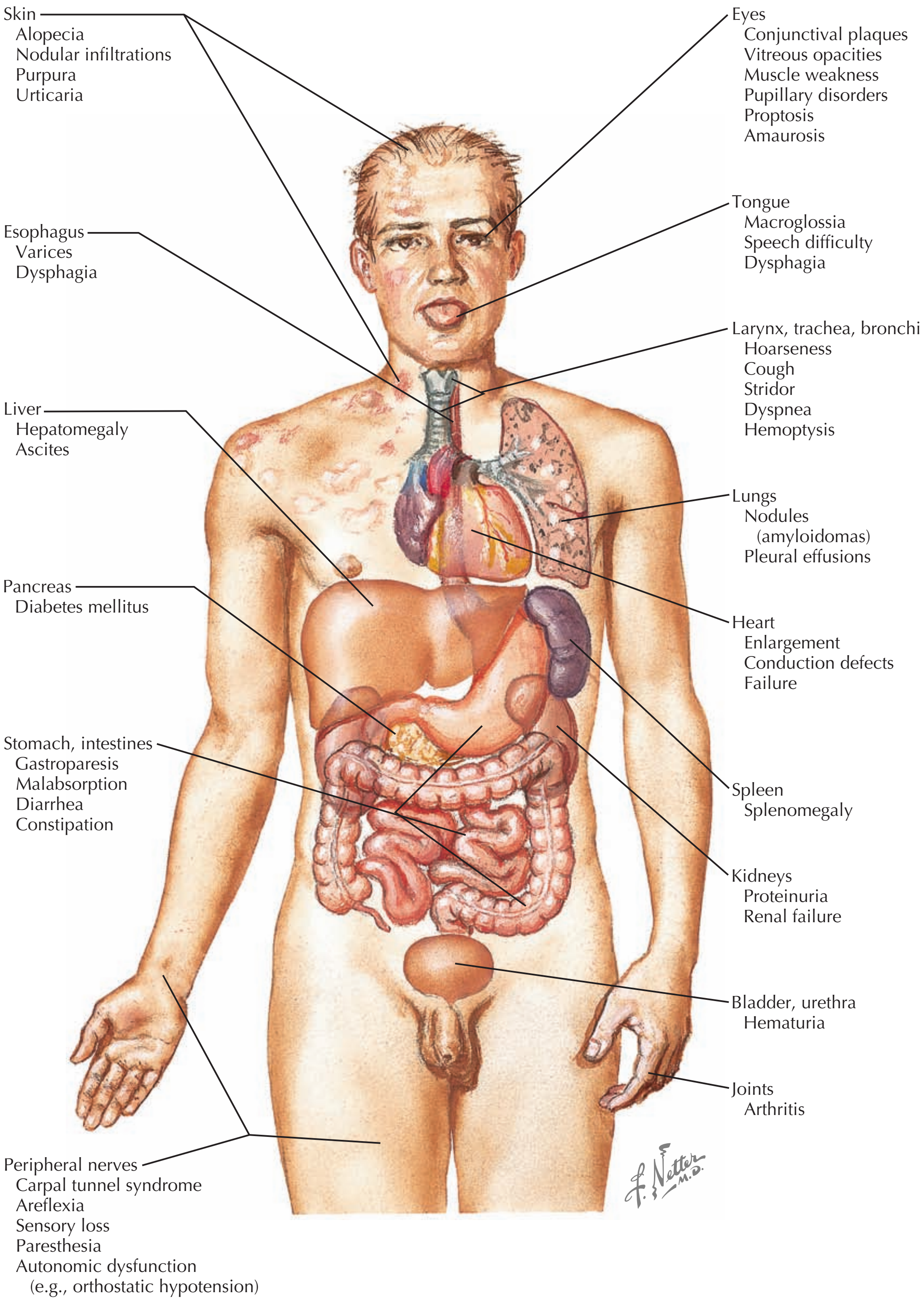
AL (primary) amyloidosis occurs in the setting of an abnormal clonal proliferation of plasma cells. During this proliferation, the light chains acquire proamyloidogenic mutations. Such mutations do not always occur when light chains are overproduced, as evidenced by the fact that only a minority of patients with multiple myeloma develop AL amyloidosis. The annual incidence of AL amyloidosis is 4.5 cases per 100,000 individuals, and it is the most common systemic amyloidosis in North America. It typically affects patients over the age of 40.

AA (secondary) amyloidosis occurs in the setting of chronic inflammatory diseases. The precursor protein is serum amyloid A (SAA), an acute phase reactant that is overproduced in chronic inflammatory states. Through a complex, incompletely understood mechanism, SAA is cleaved and undergoes a conformational change that leads to fibril formation. About half of AA amyloidosis cases are associated with rheumatoid arthritis. Other causes of secondary amyloidosis include ankylosing spondylitis, psoriatic arthritis, chronic pyogenic infections, inflammatory bowel disease, cystic fibrosis, neoplasms, and familial Mediterranean fever.

In both AA and AL amyloidosis, the renal manifestations depend on the location of fibril deposition. In the majority of renal amyloidosis cases, amyloid fibrils deposit in the glomerulus, causing proteinuria that is typically in the nephrotic range. Additional signs and symptoms are often consistent with the nephrotic syndrome (see Plate 4-7), including edema, hypercholesterolemia, and hypoalbuminemia. Renal function is usually preserved or only slightly impaired. Urine sediment may reveal lipids or fatty casts but should not contain cells or cellular casts. In a small number of cases, amyloid may deposit in the renal microvasculature, causing a slowly progressive loss of renal function without proteinuria. In even rarer cases, fibrils may deposit in the tubules, causing functional defects such as distal renal tubular acidosis, nephrogenic diabetes insipidus, or the renal Fanconi syndrome.

Both AL and AA amyloidosis may also cause disease in other organ systems. Myocardial deposition is common, resulting in signs and symptoms of restrictive cardiomyopathy. Hepatic deposition leads to hepatomegaly and abnormal liver function tests. Peripheral nervous deposition can cause sensory, motor, and autonomic abnormalities. Soft tissue deposition may manifest as macroglossia and carpal tunnel syndrome.

Deposition Sites and Manifestations of Amyloidosis


Skin
Alopecia
Nodular infiltrations
Purpura
Urticaria
Esophagus
Varices
Dysphagia
Liver
Hepatomegaly
Ascites
Pancreas
Diabetes mellitus
Stomach, intestines
Gastroparesis
Malabsorption
Diarrhea
Constipation
Peripheral nerves
Carpal tunnel syndrome
Areflexia
Sensory loss
Paresthesia
Autonomic dysfunction
(e.g., orthostatic hypotension)
Eyes
Conjunctival plaques
Vitreous opacities
Muscle weakness
Pupillary disorders
Proptosis
Amaurosis
Tongue
Macroglossia
Speech difficulty
Dysphagia
Larynx, trachea, bronchi
Hoarseness
Cough
Stridor
Dyspnea
Hemoptysis
Lungs
Nodules
(amyloidomas)
Pleural effusions
Heart
Enlargement
Conduction defects
Failure
Spleen
Splenomegaly
Kidneys
Proteinuria
Renal failure
Bladder, urethra
Hematuria
Joints
Arthritis
F. Netter M.D.

AMYLOIDOSIS *(Continued)*

PRESENTATION AND DIAGNOSIS

Amyloidosis should be on the differential diagnosis for any adult who presents with idiopathic nephrotic syndrome, especially in the presence of unexplained heart failure and peripheral and/or autonomic neuropathy. The presence of a chronic inflammatory process, such as rheumatoid arthritis, suggests possible secondary amyloidosis. A monoclonal paraprotein spike on immunofixation electrophoresis of serum or urine suggests the diagnosis of AL amyloidosis.

A tissue diagnosis is the gold standard for diagnosis, and a renal biopsy may be performed in adults with renal manifestations.

Light microscopy reveals nodular glomerulosclerosis, with deposits of amorphous material seen in the mesangium and extending into the capillary loops. The mesangial depositions can resemble Kimmelstiel-Wilson nodules seen in diabetic nephropathy, but they stain periodic acid-Schiff (PAS) more weakly. A characteristic feature of amyloid fibrils is their ability to stain with Congo Red, which causes them to exhibit characteristic apple-green birefringence under polarized light. AL and AA amyloidosis can be differentiated by immunofluorescence (IF) staining, which is positive for lambda or kappa light chains in AL amyloidosis, and for SAA in AA amyloidosis.

Electron microscopy reveals the presence of randomly organized amyloid fibrils in the mesangium and glomerular basement membrane. The fibrils are approximately 8 to 10 nm in diameter and can be differentiated from the fibrils of immunotactoid and fibrillary glomerulonephritis by their distribution and size. The fibrils in immunotactoid glomerulonephritis are composed of hollow tubules 30 to 50 nm in size, arranged in parallel stacks, whereas the fibrils in fibrillary glomerulonephritis range from 16 to 24 nm.

Somewhat less invasive diagnostic tests than a renal biopsy include abdominal fat or rectal biopsy. These are highly specific but only moderately sensitive (70% to 80%). Thus if amyloidosis is strongly suspected based on clinical history, these superficial biopsies may be performed before renal biopsy. If these tests are negative, however, renal biopsy should be performed.

If AL amyloidosis is diagnosed on tissue biopsy, bone marrow biopsy is typically performed to determine the plasma cell burden and rule out the presence of multiple myeloma and other dyscrasias.

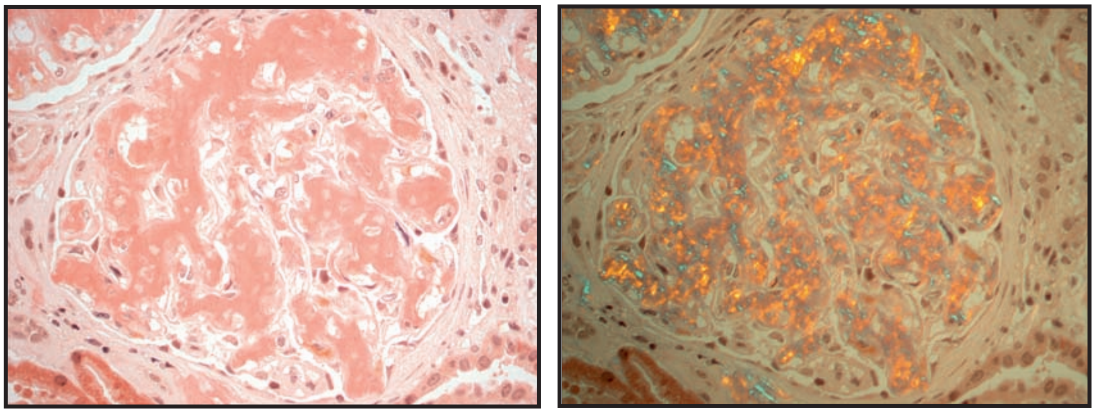
TREATMENT

In general, there are two major approaches to the treatment of amyloidosis. The most common approach is to reduce the production of precursor protein. AL production can be targeted using chemotherapy (often using some combination of melphalan, thalidomide, proteosome inhibitors, and steroids) or stem cell transplantation. AA production can be reduced by treating the underlying inflammatory disease. In rheumatoid arthritis, for example, anticytokine therapy may be helpful. In chronic infections, eradication of the focus of infection with appropriate measures, including antimicrobial agents, should be the focus.

The second approach is to destabilize the amyloid fibril by targeting its SAP or glycosaminoglycan component. An example of this approach is the compound eprodisate, which attaches to the glycosaminoglycan binding sites of amyloid fibrils in tissues, leading to fibril destabilization.

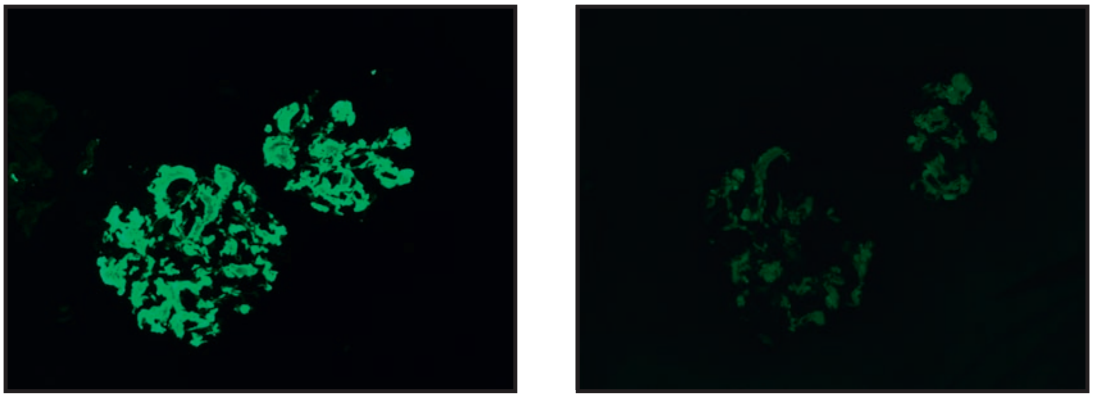
HISTOPATHOLOGIC FINDINGS OF AMYLOIDOSIS

Light microscopy findings



Nodular glomerulosclerosis with diffuse deposition of amorphous material (Congo red stain, unpolarized, 400 ×)

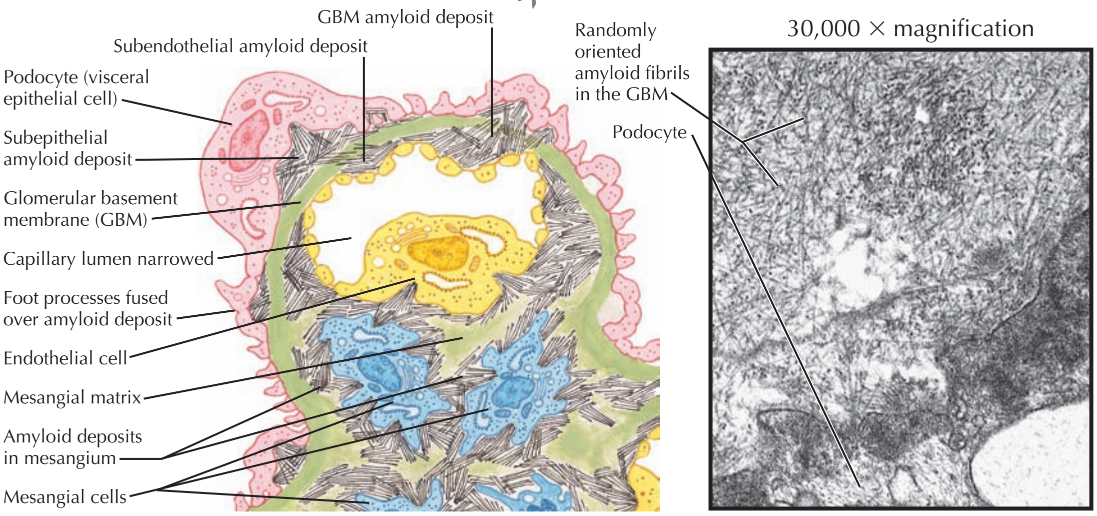
Apple-green birefringence seen under polarized light (Congo red stain, polarized, 400 ×)



Positive immunofluorescent staining for lambda light chains (40×)

Negative immunofluorescent staining for kappa light chains (40×)

Electron microscopy findings


GBM amyloid deposit
Subendothelial amyloid deposit
Podocyte (visceral epithelial cell)
Subepithelial amyloid deposit
Glomerular basement membrane (GBM)
Capillary lumen narrowed
Foot processes fused over amyloid deposit
Endothelial cell
Mesangial matrix
Amyloid deposits in mesangium
Mesangial cells
Randomly oriented amyloid fibrils in the GBM
Podocyte
30,000 × magnification

No matter how the primary disease process is treated, patients should receive conservative management for symptoms of nephrotic syndrome, including diuretics and salt restriction.

PROGNOSIS

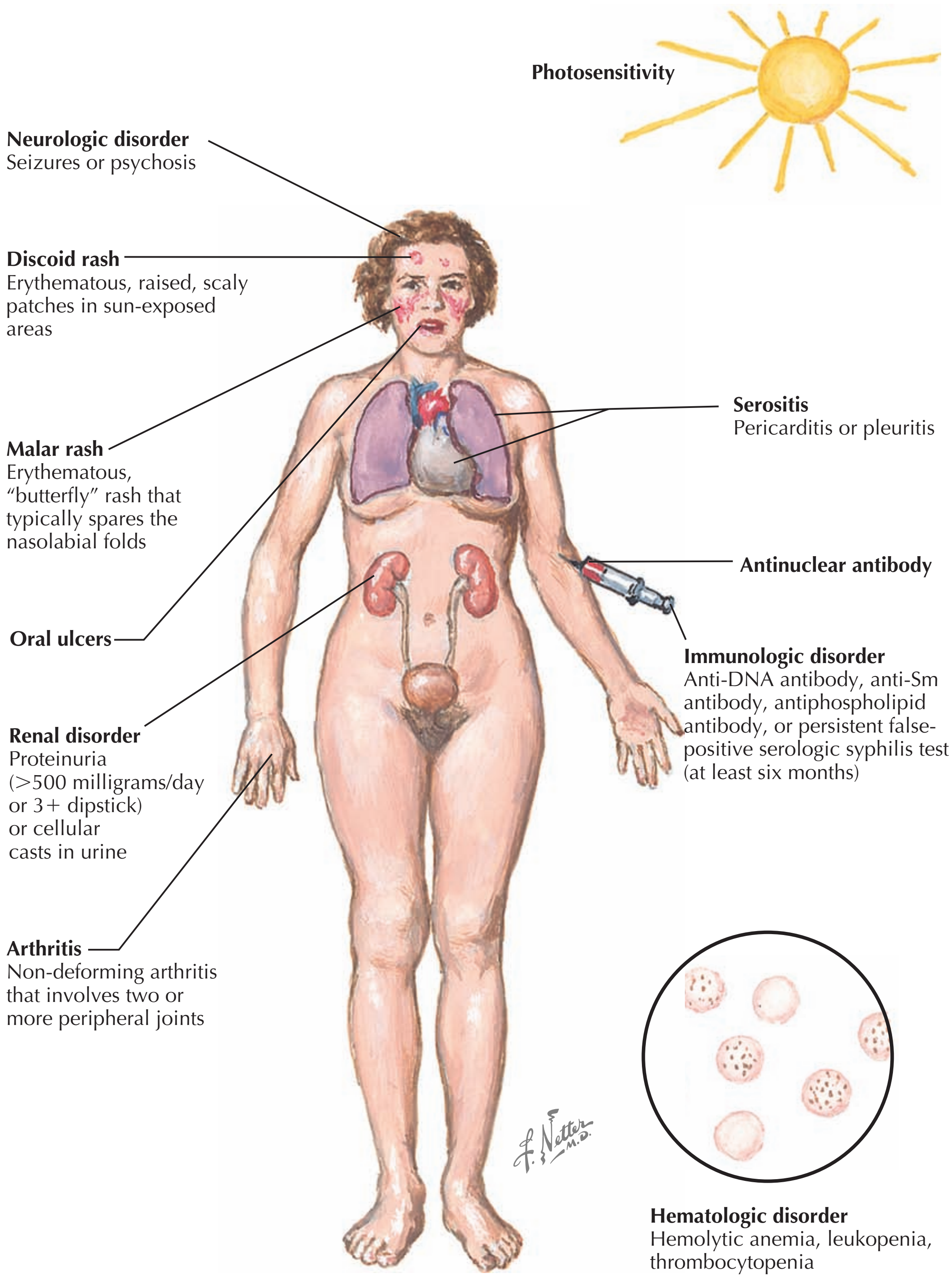
In AL amyloidosis, the prognosis depends on the degree of systemic involvement (especially cardiac involvement) and the degree to which therapy reduces free light chain production. Although AL amyloidosis was previously considered a rapidly fatal disease, patient survival appears to be increasing with current treatment regimens.

In AA amyloidosis, the prognosis depends on the activity of the underlying disease, and infections are the major cause of death. There have been well-documented cases of remission of AA amyloidosis with control of the infectious source.

LUPUS NEPHRITIS

DIAGNOSTIC CRITERIA OF SYSTEMIC LUPUS ERYTHEMATOSIS

At least four of the following must be present to establish the diagnosis.


Photosensitivity
Neurologic disorder
Seizures or psychosis
Discoid rash
Erythematous, raised, scaly patches in sun-exposed areas
Malar rash
Erythematous, "butterfly" rash that typically spares the nasolabial folds
Oral ulcers
Renal disorder
Proteinuria (>500 milligrams/day or 3+ dipstick) or cellular casts in urine
Arthritis
Non-deforming arthritis that involves two or more peripheral joints
Serositis
Pericarditis or pleuritis
Antinuclear antibody
Immunologic disorder
Anti-DNA antibody, anti-Sm antibody, antiphospholipid antibody, or persistent false-positive serologic syphilis test (at least six months)
Hematologic disorder
Hemolytic anemia, leukopenia, thrombocytopenia
F. Netter M.D.

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can involve nearly every organ system. It is predominantly a disease of young women, with a female to male ratio of roughly 10 : 1. Worldwide prevalence ranges from 10 to 160 per 100,000 persons. The incidence is highest among women of child-bearing age. It also varies by race and ethnicity, being more common in African Americans, African Caribbeans, and Asians than in Caucasians. These racial differences are likely attributable to both genetic and environmental factors. The genetic component of SLE is evidenced by its tendency to cluster in families, with monozygotic twins demonstrating a 25% concordance rate.

SLE frequently affects the kidney, causing a variety of pathologic conditions collectively known as lupus nephritis (LN). LN is a protean disease, with presentations ranging from mild urinary abnormalities to full-blown nephrotic syndrome, from smoldering chronic kidney disease to rapidly progressive glomerulonephritis.

About one in six patients with SLE will have clinically evident renal disease at the time of diagnosis, whereas 40% to 60% will develop it over time. Factors associated with increased risk of renal disease include a younger age, male gender, and non-Caucasian race.

Of note, drug-induced SLE can be nearly indistinguishable from primary SLE, but kidney involvement is rare.

PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The pathogenesis of SLE is complex and incompletely understood. It appears that a confluence of genetic, hormonal, and environmental factors promotes the development of autoantibodies. These antibodies form pathologic immune complexes that trigger complement fixation and inflammation, leading to tissue damage.

A major event in the pathogenesis of this disease is thought to be prolonged, inappropriate exposure of self-antigens to the immune system. This sensitization process is thought to occur in the context of dysregulated apoptosis or impaired phagocytic clearance of apoptotic/necrotic cells. Subsequent failure to silence autoreactive lymphocytes allows ongoing production of antibodies that bind these self-antigens.

These autoreactive antibodies typically target components of the nucleus (antinuclear antibodies, or ANA). High titers of autoantibodies against double-stranded DNA (dsDNA) are nearly pathognomonic of SLE; however, other components of the nucleosome and ribosome may also be targeted, including Sm, Ro (SS-A), La (SS-B), the complement component C1q, ribonucleoprotein (U1-RNP), and histones.

DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The American College of Rheumatology has proposed a list of 11 clinical, pathologic, and laboratory criteria that can be used to diagnose SLE. These include: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder (seizures or psychosis), hematologic disorder (cytopenias), immunologic disorder (especially anti-dsDNA or anti-Sm antibodies), and presence of ANA. Renal disorder is defined as the presence of either proteinuria (>500 mg/24 hr or 3+ protein on dipstick) or cellular casts. For research purposes, 4 of 11 criteria are required to make the diagnosis; however, in clinical practice, many patients are diagnosed with a lupus-spectrum disease without meeting this threshold.

Lupus Nephritis *(Continued)*

PATHOGENESIS OF LUPUS NEPHRITIS

The renal disease associated with SLE often results from inflammation of the glomerulus. SLE may also cause tubulointerstitial disease, however, as well as microvascular disease that resembles thrombotic thrombocytopenic purpura (see Plate 4-34), especially in association with antiphospholipid antibodies.

The exact process by which autoantibodies in SLE cause glomerular disease is poorly understood. For example, it is unclear if the autoantibodies cross-react with glomerular antigens, or if they first form circulating antigen-antibody complexes that subsequently deposit in the glomerulus. In either case, the presence of the immune complexes leads to ongoing glomerular inflammation.

PRESENTATION AND DIAGNOSIS OF LUPUS NEPHRITIS

The clinical findings in lupus nephritis are variable. Among affected patients, nearly 100% will have proteinuria, 80% will have microscopic hematuria, 45% to 65% will have the full nephrotic syndrome, and 40% to 80% will have reduced renal function. Supportive diagnostic tests include positive ANA and anti-dsDNA antibodies, as well as abnormally low levels of circulating complement (both C3 and C4).

Once the presence of lupus nephritis is clinically evident, proper management often requires further characterization of the glomerular lesion. Although the clinical signs sometimes correlate with the nature and extent of glomerular disease, these associations are unreliable. For example, a given level of azotemia may reflect either active, reversible proliferative nephritis, or a burnt-out, sclerosed kidney without active disease. In the former, aggressive immunosuppression may markedly ameliorate kidney function; in the latter, it will impart no benefit and subject the patient to needless risk. Thus a kidney biopsy is often essential to clarify the disease process and guide management. The major indications for this procedure include abnormal or increasing proteinuria (>500 mg/24 hr), an active urinary sediment, or renal insufficiency.

Based on histopathologic findings, the glomerular lesions of LN can be divided into six basic classes using criteria defined by the International Society of Nephrology and Renal Pathology Society (ISN/RPS). They are:

Class I—Minimal mesangial lupus nephritis
Class II—Mesangial proliferative lupus nephritis
Class III—Focal lupus nephritis
Class IV—Diffuse lupus nephritis
Class V—Membranous lupus nephritis
Class VI—Advanced sclerosing lupus nephritis

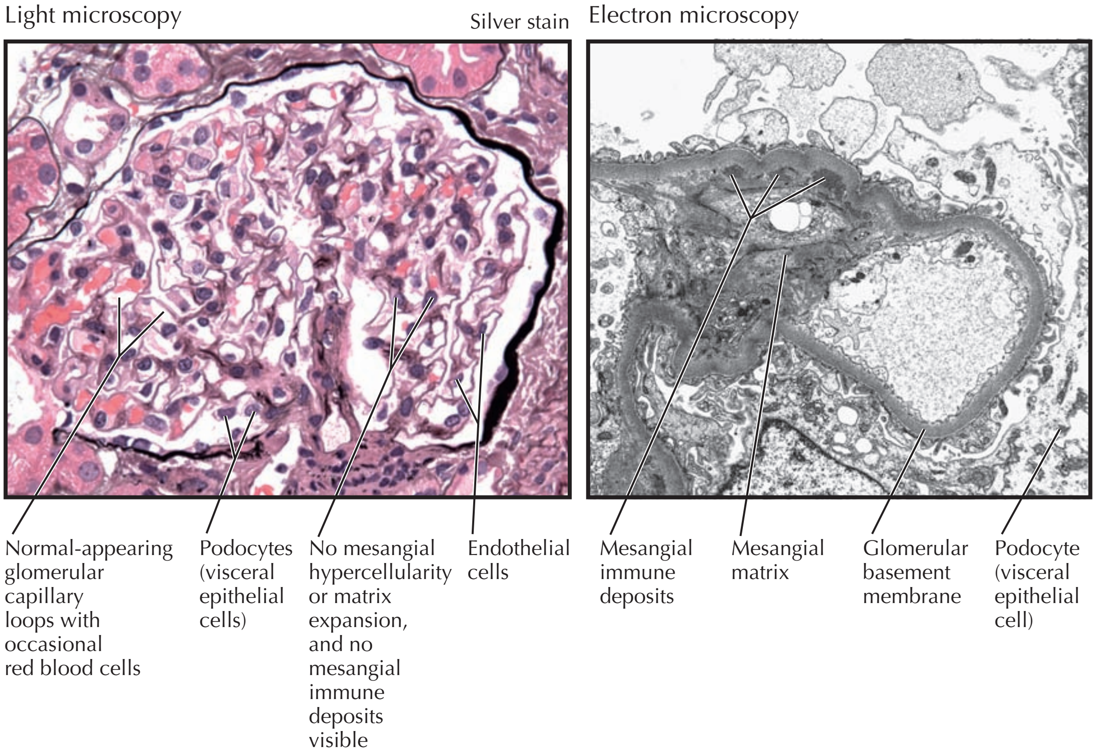
In general, classes I and II reflect immune complex deposition localized to the mesangium; classes III and IV reflect additional deposition in the subendothelium; and class V reflects deposition predominantly in the subepithelium. Class VI is an advanced, sclerotic state with no ongoing inflammation.

No single histologic feature is consistent across all classes or considered pathognomonic for LN; however, "full house" staining of the glomerulus on immunofluorescence is highly characteristic. It is defined as positive staining for three immunoglobulins (IgG, IgM, and IgA) in addition to complement components C3 and C1q. Likewise, the presence of tubulo-reticular inclusions in endothelial cells on electron microscopy is suggestive, but not pathognomonic, of LN. These inclusions are thought to develop in response to elevated interferon levels and are also common in HIV-associated nephropathy. The other histologic features depend on the disease class.

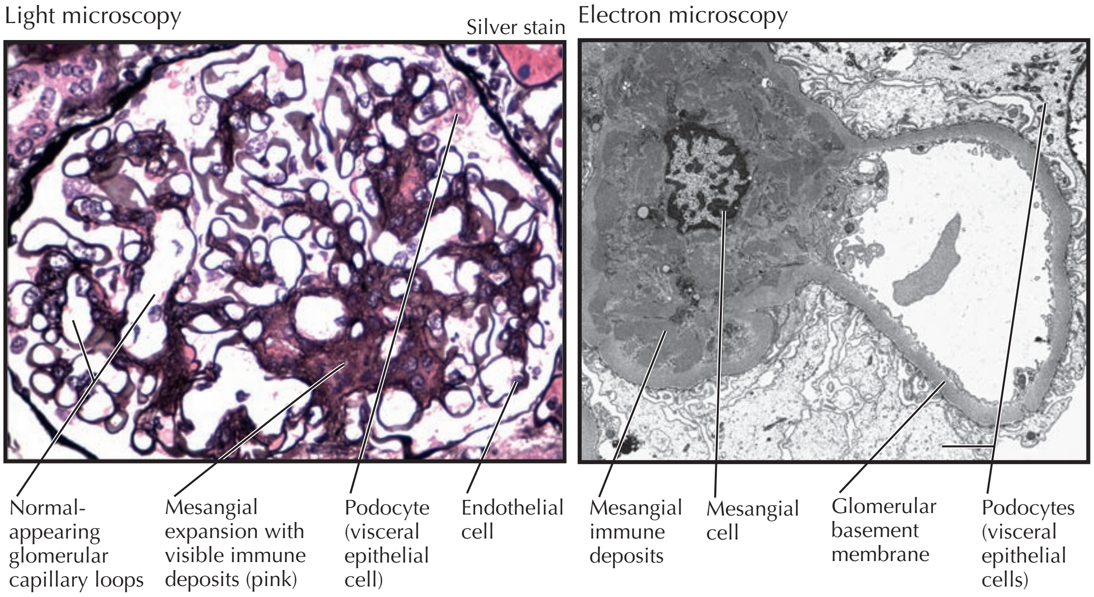
In class I ("minimal mesangial LN") mesangial immune deposits are seen on immunofluorescence or electron microscopy but not on light microscopy.

Renal Histopathology (Classes I and II Lesions) of Systemic Lupus Erythematosus

Class I lesion

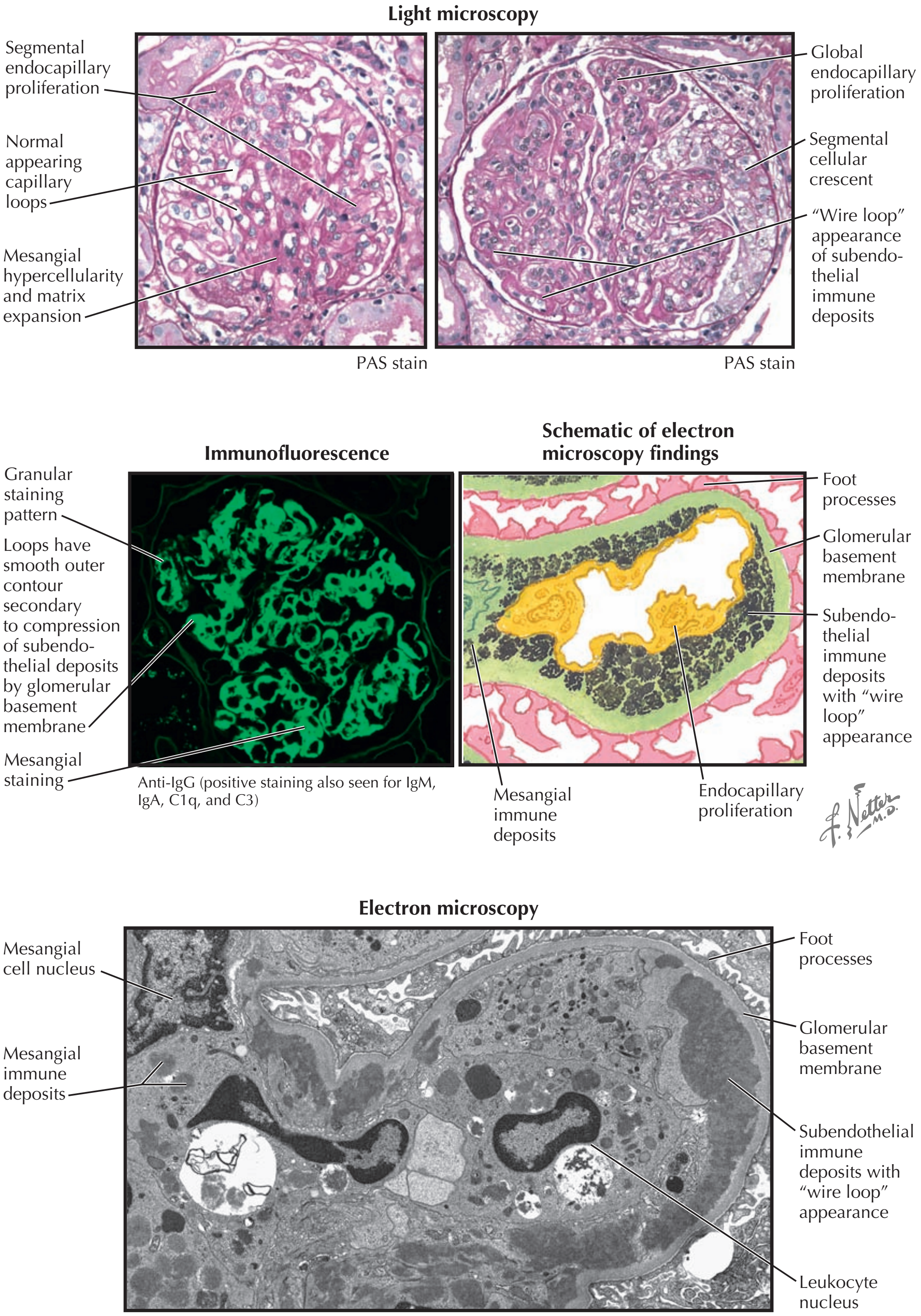

Light microscopy
Silver stain
Electron microscopy
Normal-appearing glomerular capillary loops with occasional red blood cells
Podocytes (visceral epithelial cells)
No mesangial hypercellularity or matrix expansion, and no mesangial immune deposits visible
Endothelial cells
Mesangial immune deposits
Mesangial matrix
Glomerular basement membrane
Podocyte (visceral epithelial cell)

Class II lesion


Light microscopy
Silver stain
Electron microscopy
Normal-appearing glomerular capillary loops
Mesangial expansion with visible immune deposits (pink)
Podocyte (visceral epithelial cell)
Endothelial cell
Mesangial immune deposits
Mesangial cell
Glomerular basement membrane
Podocytes (visceral epithelial cells)

(Immunofluorescence not shown but reveals "full-house" staining of mesangial immune deposits in both classes I and II lesions.)

RENAL HISTOPATHOLOGY (CLASSES III AND IV LESIONS) OF SYSTEMIC LUPUS ERYTHEMATOSUS


Light microscopy
Segmental endocapillary proliferation
Normal appearing capillary loops
Mesangial hypercellularity and matrix expansion
PAS stain
Global endocapillary proliferation
Segmental cellular crescent
"Wire loop" appearance of subendothelial immune deposits
PAS stain
Immunofluorescence
Granular staining pattern
Loops have smooth outer contour secondary to compression of subendothelial deposits by glomerular basement membrane
Mesangial staining
Anti-IgG (positive staining also seen for IgM, IgA, C1q, and C3)
Schematic of electron microscopy findings
Foot processes
Glomerular basement membrane
Subendothelial immune deposits with "wire loop" appearance
Mesangial immune deposits
Endocapillary proliferation
Electron microscopy
Mesangial cell nucleus
Mesangial immune deposits
Foot processes
Glomerular basement membrane
Subendothelial immune deposits with "wire loop" appearance
Leukocyte nucleus

LUPUS NEPHRITIS *(Continued)*

There is a relative lack of inflammation, and glomeruli appear normal under light microscopy. Patients generally have normal renal function and an unremarkable urine sediment. Thus biopsies are rarely (if ever) taken.

In class II ("mesangial proliferative LN"), in contrast, there are visible mesangial immune deposits on light microscopy that are associated with mesangial hypercellularity and/or matrix expansion. Although a few isolated subepithelial or subendothelial immune deposits may be visible by immunofluorescence or electron microscopy, none should be present on light microscopy. These lesions typically cause microhematuria and subnephrotic proteinuria. Overall renal function remains intact, however, and hypertension is rare.

In class III ("focal LN"), subendothelial immune deposits are seen on electron or light microscopy, typically in a focal pattern, and are associated with segmental or global endocapillary or extracapillary glomerulonephritis that involves <50% of all glomeruli. ("Segmental" indicates that only part of a glomerulus is involved, whereas "global" indicates the entire glomerulus is involved.) Mesangial alterations, such as hypercellularity or mesangial immune deposits, may or may not be present.

Class III is further specified as "A" or "C" to indicate the presence of active (proliferative) or chronic (sclerosing) lesions. Active lesions are those with evidence of ongoing inflammation, such as hypercellularity, karyorrhexis, fibrinoid necrosis, and cellular crescents. In contrast, chronic lesions consist of tissue that has generally undergone irreversible scarring, with features such as glomerulosclerosis, fibrous adhesions, and fibrous crescents.

In class IV ("diffuse LN"), the lesions are qualitatively similar to those of Class III but involve 50% or more of all glomeruli. In addition, there is often a more diffuse distribution of the subendothelial immune deposits. When the subendothelial deposits are prominent enough to be seen by light microscopy, they impart a classic "wire-loop" appearance to the glomerular capillaries. As in class III, mesangial alterations may or may not be present.

Class IV is further subdivided into diffuse segmental (IV-S) LN when 50% or more of the involved glomeruli have segmental lesions, or diffuse global (IV-G) LN when 50% or more of the involved glomeruli have global lesions. The "A" and "C" modifiers are again used to designate active or chronic lesions.

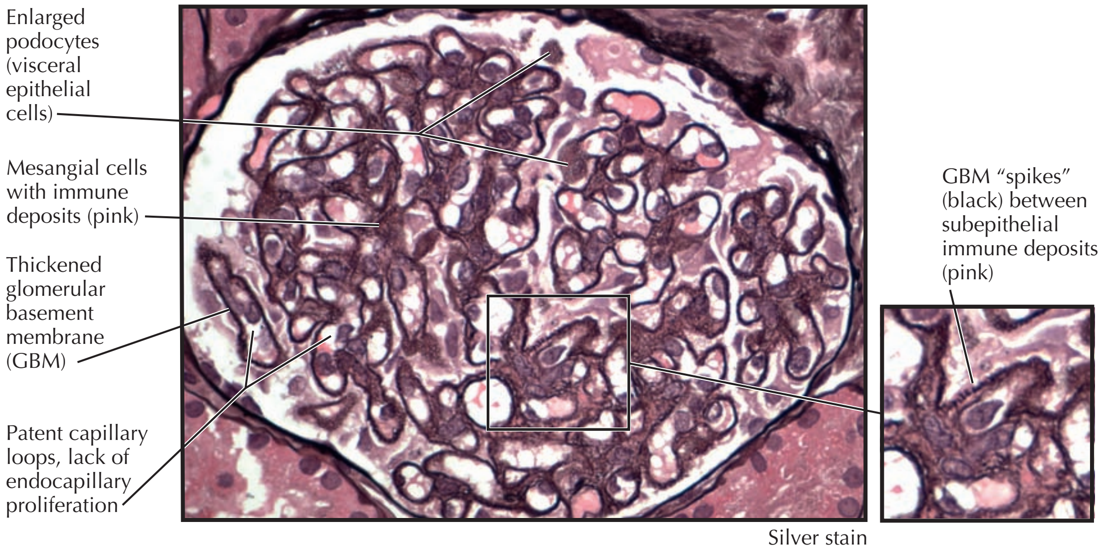
Patients with class III or IV lesions often have prominent clinical manifestations including glomerular hematuria, marked proteinuria, hypertension, and renal insufficiency. Urine sediment often contains dysmorphic RBCs and red blood cell casts.

In class V ("membranous LN"), there is a global or segmental distribution of subepithelial immune deposits (or their morphologic sequelae), which are visible on light microscopy along with either immunofluorescence or electron microscopy. The subepithelial changes associated with immune complex deposition resemble those of primary membranous nephropathy (see Plate 4-13); however, unlike in primary membranous nephropathy, membranous LN frequently features mesangial immune complex deposits as well.

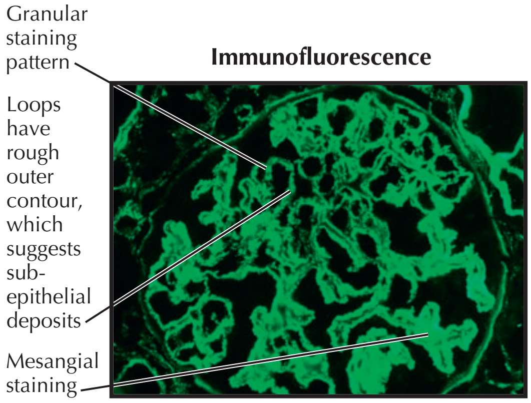
Because the subepithelium is a major component of the protein diffusion barrier, patients with type V disease usually have more severe proteinuria than those with the other disease classes. Frank nephrotic syndrome is common and increases the risk of thromboembolic disease. In up to 40% of patients, however, proteinuria remains subnephrotic. Because circulating immune cells do not have access to the subepithelial antibodies, in pure class V LN the urine sediment is typically less active than in class III or IV disease. Note, however, that class V disease can occur in combination with class III or IV disease.

Renal Histopathology (Class V Lesions) of Systemic Lupus Erythematosus

Light microscopy

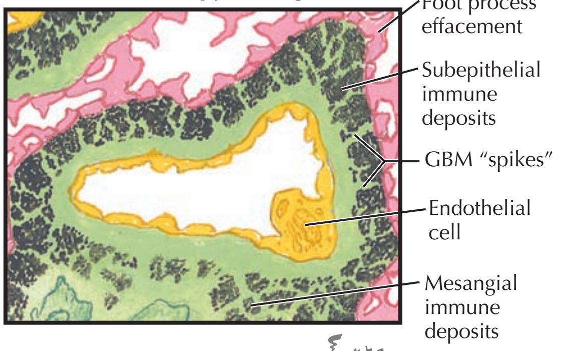

Enlarged podocytes (visceral epithelial cells)
Mesangial cells with immune deposits (pink)
Thickened glomerular basement membrane (GBM)
Patent capillary loops, lack of endocapillary proliferation
GBM “spikes” (black) between subepithelial immune deposits (pink)
Silver stain

Immunofluorescence

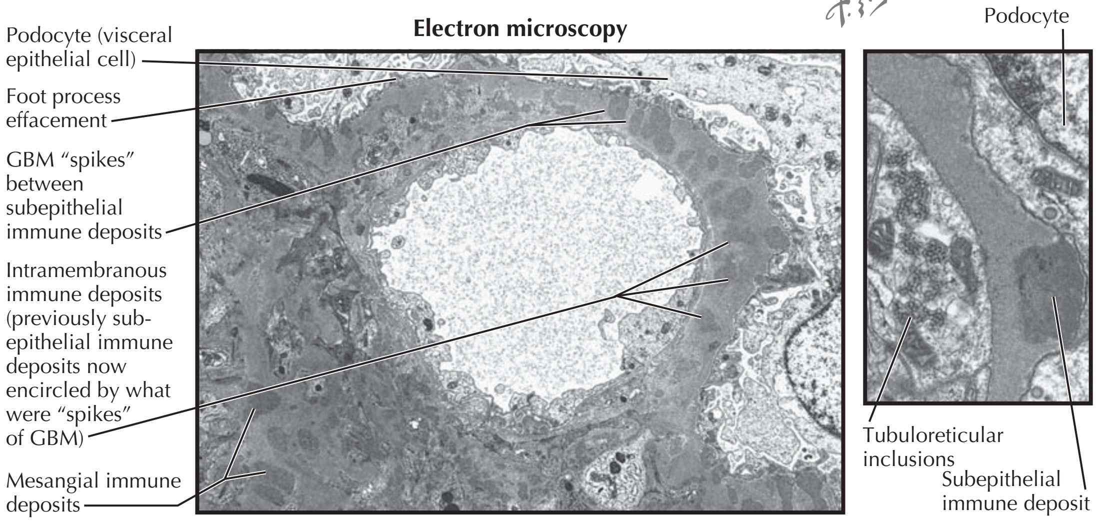

Granular staining pattern
Loops have rough outer contour, which suggests sub-epithelial deposits
Mesangial staining

Anti-IgG (positive staining also seen for IgM, IgA, C1q, and C3)

Schematic of electron microscopy findings


Foot process effacement
Subepithelial immune deposits
GBM “spikes”
Endothelial cell
Mesangial immune deposits

Electron microscopy


Podocyte (visceral epithelial cell)
Foot process effacement
GBM “spikes” between subepithelial immune deposits
Intramembranous immune deposits (previously sub-epithelial immune deposits now encircled by what were “spikes” of GBM)
Mesangial immune deposits
Podocyte
Tubuloreticular inclusions
Subepithelial immune deposit

LUPUS NEPHRITIS *(Continued)*

In class VI (“advanced sclerosing LN”), 90% or more of glomeruli are globally sclerosed. Though active immune damage is no longer occurring, prior inflammation has irreparably damaged nearly every functioning nephron. This class represents an end-stage kidney, the eventual sequela of untreated or refractory LN. Patients will invariably have significantly impaired renal function that will not benefit from immunosuppression.

The relative frequency of these classes varies across studies based on geographic location, patient makeup, and local biopsy practices. For example, a study of 92 Japanese patients found the following breakdown: class I (minimal mesangial LN) 0%, class II (mesangial proliferative LN) 13%, class III (focal LN) 17%, class IV (diffuse LN) 60%, and class V (membranous LN) 10%. It must be noted that patients with SLE may experience several different types of LN at different times over the course of their disease, and rebiopsy is warranted if the clinical picture changes.

TREATMENT

All patients with proteinuria, irrespective of the histologic class, should be treated with ACE inhibitors or ARBs. Hypertension should be strictly controlled. Hyperlipidemia should also be treated if present, which may require the use of a statin drug. The use of nonsteroidal antiinflammatory drugs should be assessed and, if present, limited. Prolonged or unprotected exposure to sunlight should be rigorously avoided because it can trigger lupus flares.

Pharmacologic immunosuppression is often not required for class I or II disease. In contrast, in class III or class IV disease, there is a higher risk for progressive loss of kidney function that mandates more aggressive treatment. The two drugs best studied for induction therapy are pulse cyclophosphamide and mycophenolate. Either one is initiated in conjunction with high-dose corticosteroids. The preponderance of data from clinical trials suggests that the two regimens are equivalent in achieving remission, usually at rates of 60% to 80%. Maintenance of remission can be obtained with mycophenolate or azathioprine.

The treatment of membranous (class V) LN is controversial. All patients should receive treatment for proteinuria. Immunosuppressive regimens involving corticosteroids in conjunction with cyclophosphamide, cyclosporine, or mycophenolate have all been tried with varying results. It appears that combination regimens are superior to corticosteroids alone.

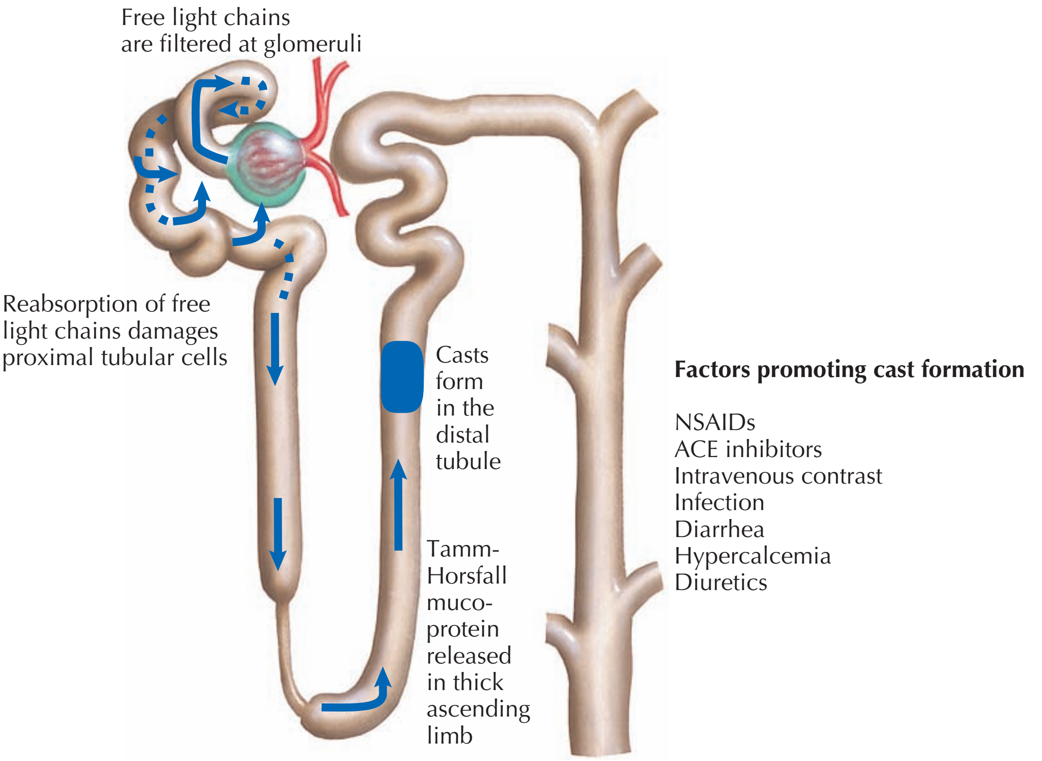
PROGNOSIS

The overall survival of patients with LN has improved over the last half century, with 5-year survival rates increasing from 50% in the 1940s and 1950s to more than 90% since the 1990s. Nevertheless, disease-wide outcomes remain unsatisfactory. Nearly 50% of patients treated for LN will eventually have relapse of their symptoms. In addition, a significant number of patients will be unable to tolerate treatment, suffer serious adverse events from immunosuppression, or have disease that is refractory to therapy. End-stage renal disease (ESRD) eventually occurs in 10% to 15% of patients.

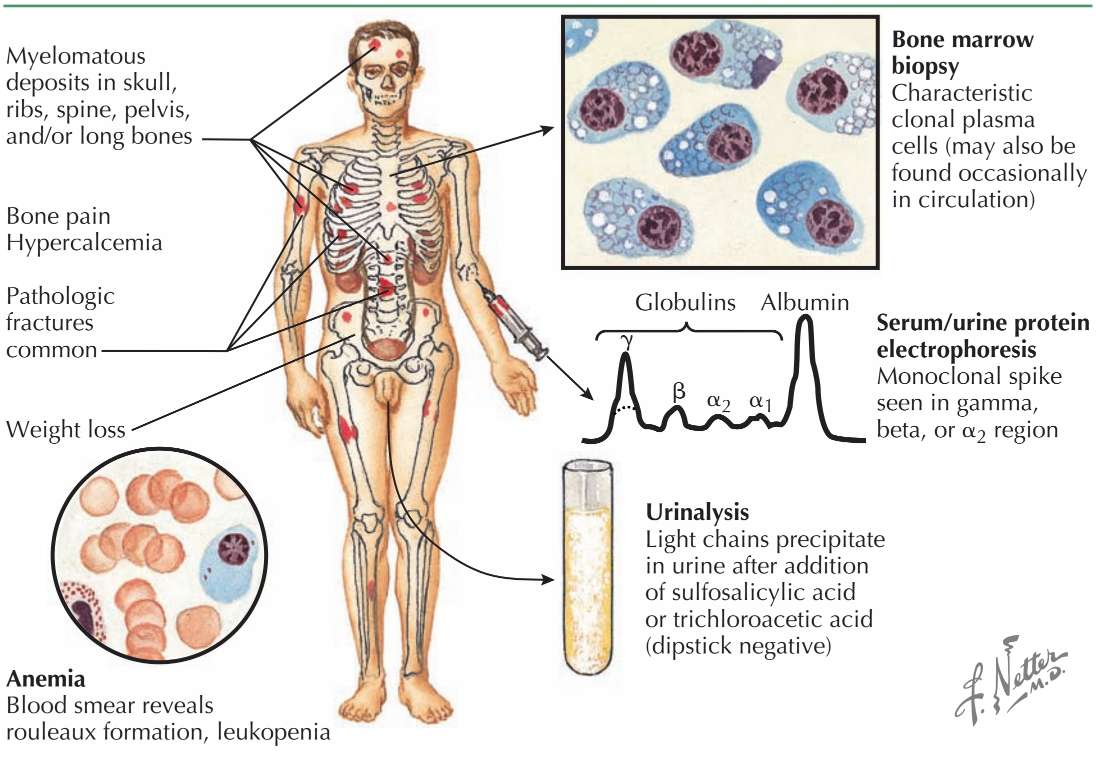
Once a patient progresses to ESRD, the systemic manifestations of SLE will often abate over a period of months, perhaps because the loss of nephrons eliminates an important source of autoantigens. Kidney transplant is a viable option with generally excellent outcomes. Recurrence of LN in the allograft develops in less than 10% of cases and very rarely causes allograft loss.

PATHOPHYSIOLOGY AND CLINICAL FINDINGS OF MYELOMA NEPHROPATHY

Mechanisms of cast nephropathy


Free light chains are filtered at glomeruli
Reabsorption of free light chains damages proximal tubular cells
Casts form in the distal tubule
Tamm-Horsfall mucoprotein released in thick ascending limb
Factors promoting cast formation
NSAIDs
ACE inhibitors
Intravenous contrast
Infection
Diarrhea
Hypercalcemia
Diuretics

Presentation and diagnostic findings


Myelomatous deposits in skull, ribs, spine, pelvis, and/or long bones
Bone pain
Hypercalcemia
Pathologic fractures common
Weight loss
Anemia
Blood smear reveals rouleaux formation, leukopenia
Bone marrow biopsy
Characteristic clonal plasma cells (may also be found occasionally in circulation)
Globulins
Albumin
γ
β
α_2
α_1
Serum/urine protein electrophoresis
Monoclonal spike seen in gamma, beta, or α_2 region
Urinalysis
Light chains precipitate in urine after addition of sulfosalicylic acid or trichloroacetic acid (dipstick negative)

MYELOMA NEPHROPATHY

Multiple myeloma is a malignant disorder of plasma cells that features clonal proliferation of a single immunoglobulin-producing cell. These plasma cell clones hypersecrete monoclonal (M) proteins, which can be either intact immunoglobulins, usually of the IgG or IgA type, or free κ or λ light chains (known as Bence-Jones proteins). The disease is generally diagnosed during the sixth decade of life, and up to half of patients will experience renal complications. Renal disease typically occurs as a result of the hypersecretion of free light chains, which have a direct toxic effect on the kidneys; however, urate nephropathy and direct plasma cell infiltration of the renal parenchyma can occur as well.

PATHOPHYSIOLOGY

Plasma cells normally release a modest excess of free light chains that are excreted in urine at the rate of 10 to 30 mg/day. These proteins are filtered at the glomerulus, and the majority are reabsorbed by proximal tubular cells and subsequently catabolized.

In multiple myeloma, light chains may be present in such overwhelming excess that they overcome the reabsorptive capacity of the nephrons. The high concentrations of light chains in the tubular lumina may in turn lead to a phenomenon known as “cast nephropathy.” Injury occurs through two mechanisms. First, light chains form obstructive casts that can cause acute or chronic renal failure. Second, light chains accumulate in proximal tubule cells because of resistance to degradation, which leads to tubular epithelial cell injury (and, in turn, impaired proximal light chain reabsorption and increased delivery to the distal tubule).

The formation of light chain casts is dependent on several factors. First, the light chains must reach a threshold concentration. Second, the light chains must bind to Tamm-Horsfall protein, normally produced in the thick ascending limb. Light chain casts are thus usually found in the distal tubule because of the increased light chain concentration in this segment (secondary to fluid reabsorption in more proximal segments), as well as the presence of Tamm-Horsfall protein.

Several factors can precipitate cast nephropathy in a patient with myeloma. Many of these factors either reduce glomerular filtration rate (GFR) or slow the rate of distal tubular fluid delivery, thereby raising the concentration of tubular light chains and favoring cast formation. For example, NSAIDs, ACE inhibitors, intravenous contrast, and infection can precipitate cast nephropathy, likely by decreasing GFR. Likewise, diarrheal illness, hypercalcemia, and diuretics are precipitants that likely act by causing volume depletion.

Less commonly, the M proteins may deposit in the glomerulus, where they disrupt the protein filtration barrier (e.g., light chain deposition disease, amyloidosis, and immunotactoid glomerulonephritis). In addition, the light chains may sometimes cause extensive damage to the proximal tubule, resulting in more generalized reabsorption defects (renal Fanconi syndrome).

PRESENTATION AND DIAGNOSIS

Nearly 50% of patients with myeloma cast nephropathy have acute kidney injury; the remaining cases are either subacute or chronic. A typical presentation in a patient without known myeloma is several weeks of oliguria, weakness, fatigue, lethargy, and lower extremity edema with newly diagnosed severe renal insufficiency. In contrast, a patient with a known myeloma diagnosis will often be noted to have an asymptomatic rise in creatinine on routine laboratory evaluation. Some of the known precipitants, listed previously, may be noted in the recent clinical history.

MYELOMA NEPHROPATHY

(Continued)

On further evaluation, patients will be found to have bland urine sediment, minimal dipstick proteinuria, and subnephrotic-range proteinuria on a quantitative collection. The dipstick measurement of proteinuria is generally unremarkable because it detects only albumin, whereas these patients excrete large quantities of light chains. Photometry of a urine specimen after the addition of a precipitant such as sulfosalicylic acid or trichloroacetic acid, however, will reveal the presence of all urine proteins. More than a gram of protein on a quantitative photometric urine specimen with a negative dipstick for albumin is suggestive of paraproteinuria. Immunofixation electrophoresis of serum and urine should be performed to confirm and identify the paraproteins.

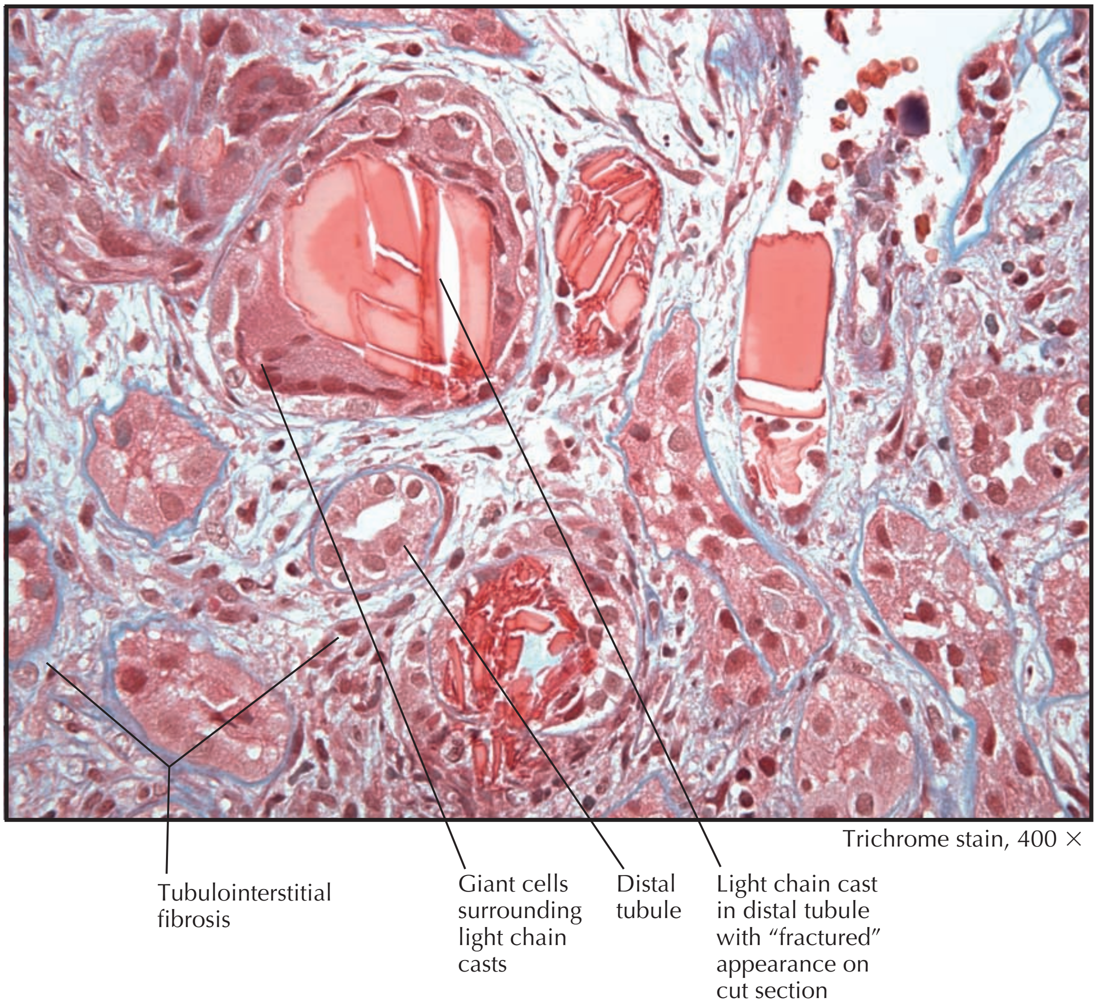
In contrast, a strongly positive dipstick and nephrotic-range proteinuria in the setting of myeloma suggests AL amyloidosis or light chain deposition disease, since these conditions cause glomerular injury that allows albumin to enter the urinary space.

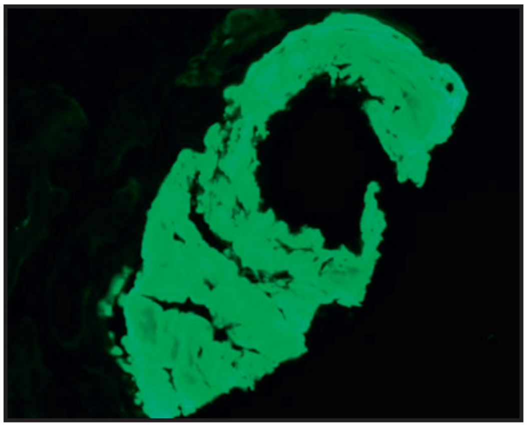
The definitive diagnosis of myeloma depends on the observation of a monoclonal protein on serum or urine protein electrophoresis, demonstration of 10% or more clonal plasma cells on bone marrow biopsy, and evidence of organ damage. Recently, the ability to quantify free light chains has provided a more sensitive diagnostic modality. In multiple myeloma and other monoclonal gammopathies, overexpression of κ or λ restricted light chains causes the κ:λ free light chain ratio to become abnormal.

Although cast nephropathy is highly probable in a patient with confirmed myeloma who has renal failure, a bland sediment, and minimal albuminuria, a definitive diagnosis requires renal biopsy.

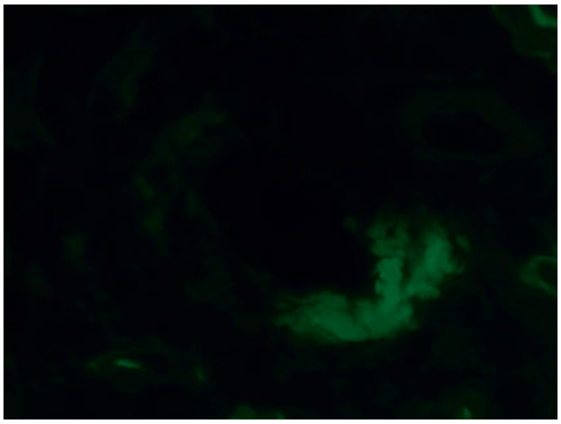
The exact indications for renal biopsy are controversial. If one is performed, characteristic findings include intratubular casts that have a "fractured" appearance, with adjacent reactive cells that include multinucleated giant cells. On immunofluorescence, these casts stain only for κ or λ light chains, which corresponds to the abnormal light chain. Patients with more chronic disease may have a variable degree of tubulointerstitial fibrosis.

HISTOPATHOLOGIC FINDINGS OF MYELOMA NEPHROPATHY


Trichrome stain, 400 ×
Tubulointerstitial fibrosis
Giant cells surrounding light chain casts
Distal tubule
Light chain cast in distal tubule with "fractured" appearance on cut section



Immunoflurorescence targeting lambda light chains



Immunoflurorescence targeting kappa light chains

TREATMENT

Treatment of myeloma cast nephropathy centers on volume expansion, which reduces intratubular cast concentration, as well as chemotherapy (and sometimes plasmapheresis), which reduces serum free light chain concentration. The role of plasmapheresis is controversial. One study of patients with biopsy-proven myeloma cast nephropathy found that plasmapheresis led to a 50% reduction in serum creatinine concentration, as well as dialysis independence, in those who experienced a more than 50% reduction in the serum free light chain concentration. Other studies, however, have shown no benefit. Dialysis is offered to patients who have advanced renal failure as a supportive measure, but it does not influence the course of the disease.

PROGNOSIS

Survival in patients with multiple myeloma is inversely correlated with serum creatinine concentration at presentation, as shown in a study from the 1980s that found a median survival of 44, 18, and 4.3 months in patients with creatinine less than 1.4, 1.4 to 2.0, and greater than 2.0 mg/dL, respectively. The potential for improvement of renal function in response to treatment correlates best with the degree of tubulointerstitial fibrosis and tubular atrophy on biopsy. Recovery of renal function has been known to occur in patients who require dialysis, occuring up to 3 months after dialysis onset.

HIV-Associated Nephropathy

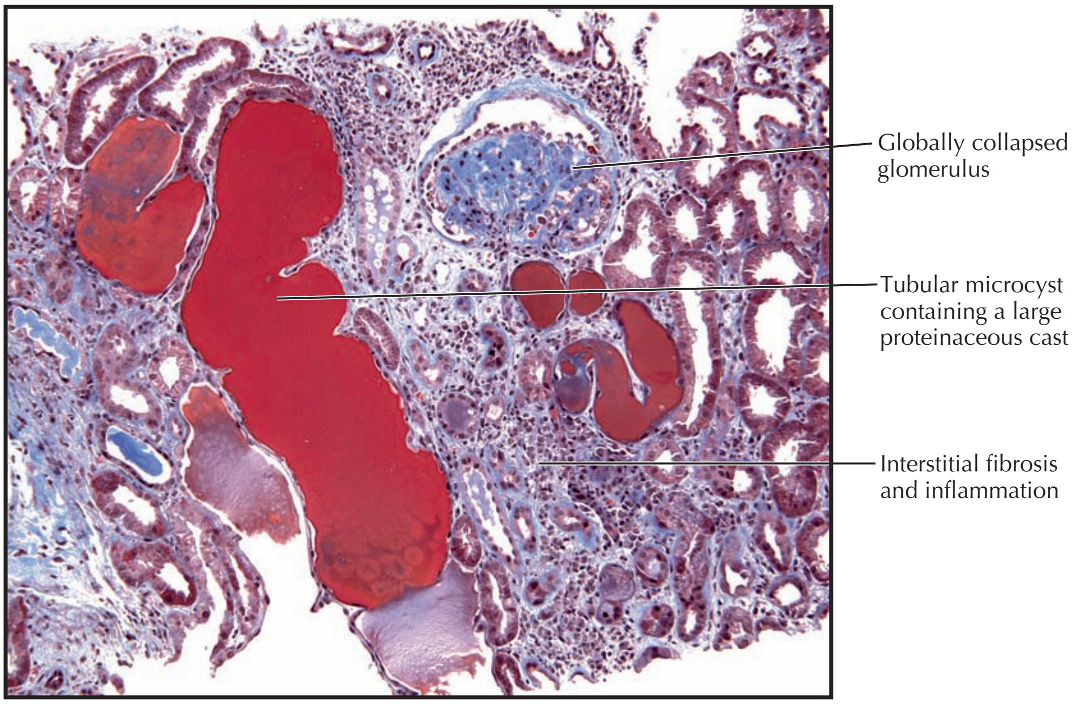
Several years after the emergence of the acquired immunodeficiency syndrome (AIDS) epidemic in the early 1980s, an association with renal disease was recognized. By 1984, reports described a distinctive form of focal segmental glomerulosclerosis (FSGS) in African Americans and Haitian immigrants with AIDS living in the large urban centers of New York and Miami. This new disease, initially called AIDS nephropathy, is now termed human immunodeficiency virus (HIV)-associated nephropathy (HIVAN) because the essential feature is infection with the HIV-1 virus, not the full clinical constellation of AIDS.

At present, approximately 800 to 900 new cases of HIVAN are reported to the U.S. Renal Database System (USRDS) each year. HIVAN is approximately tenfold more common in blacks than whites, indicating a strong racial predisposition based on genetic factors. It is clinically characterized by progressive renal insufficiency, often accompanied by proteinuria, nephrotic syndrome, and the ultrasonographic findings of enlarged, hyperechoic kidneys. The clinical picture reflects virus-mediated podocyte injury and proliferation, which leads to collapsing focal segmental glomerulosclerosis with microcystic dilation of the tubules and interstitial fibrosis and inflammation.

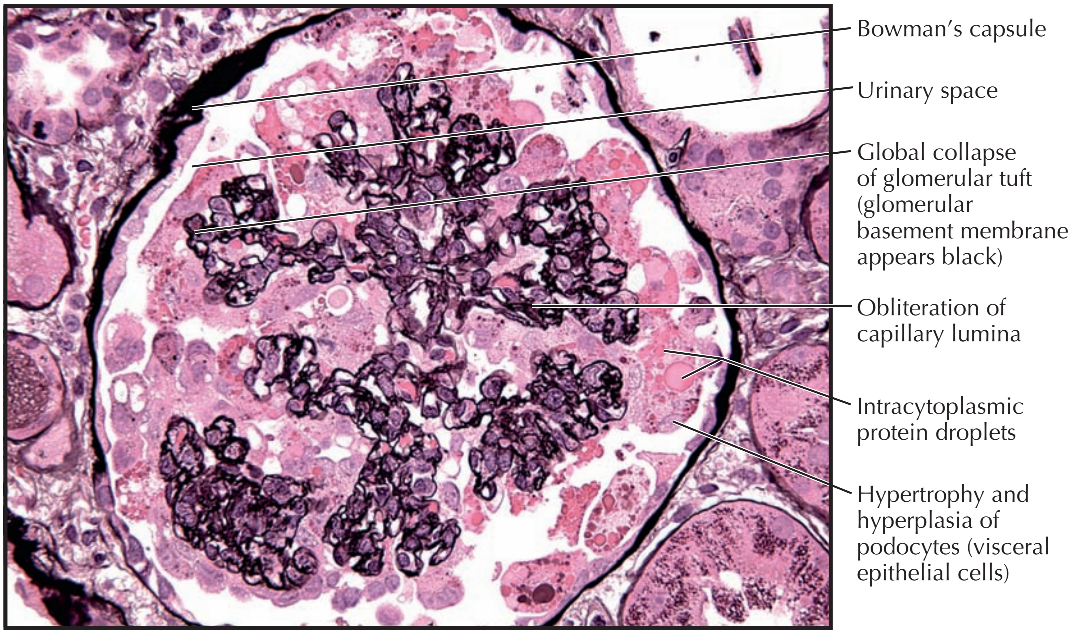
In the early years of the epidemic, before effective therapy, progression to end-stage renal disease (ESRD) or death was nearly universal, and by 1999 "AIDS nephropathy" had become the third leading cause of ESRD among adult African Americans aged 20 to 64 years. The widespread availability of combination antiretroviral therapy to treat HIV-1 infection, however, has changed the natural history and epidemiology of HIVAN. The incidence of new cases of HIVAN has been reduced and the rate of progression to renal failure has been slowed by antiretroviral therapy, which is now the mainstay of treatment.

Following the introduction of combination antiretroviral therapy, the incidence of ESRD attributed to HIVAN has reached a plateau in the United States; however, because HIV-infected patients are living longer with nephropathy, the prevalence of HIV-related ESRD continues to increase. Given a stable annual mortality rate and assuming a linear growth of the HIV epidemic among African Americans, it is projected that nearly 10,000 patients in the United States will be living with ESRD due to HIVAN by the year 2020. Emerging data from African populations indicate a high prevalence of kidney disease among HIV-infected individuals in sub-Saharan Africa, reaching 38% in Nigeria. As antiretroviral therapy becomes more available worldwide, it is likely that an increasing number of HIV-infected Africans will also be living with ESRD due to HIVAN.

Light Microscopy Findings of HIV-Associated Nephropathy


Globally collapsed glomerulus
Tubular microcyst containing a large proteinaceous cast
Interstitial fibrosis and inflammation

Trichrome stain


Bowman's capsule
Urinary space
Global collapse of glomerular tuft (glomerular basement membrane appears black)
Obliteration of capillary lumina
Intracytoplasmic protein droplets
Hypertrophy and hyperplasia of podocytes (visceral epithelial cells)

Silver stain

PATHOPHYSIOLOGY

HIVAN is caused by direct infection of renal epithelial cells by the HIV-1 virus, leading to viral gene expression. RNA in situ hybridization and DNA in situ polymerase chain reaction amplification of specific HIV-1 genes from human renal biopsies have detected HIV-1 virus in the podocytes (glomerular visceral epithelial cells), the parietal epithelial cells lining Bowman's capsule, and tubular epithelial cells. Individual patients are noted to have different HIV-1 quasispecies in their renal epithelium compared with their peripheral blood leukocytes, indicating the ability of the virus to replicate and undergo mutation within the renal epithelium. This process of error-prone viral replication allows the virus to change its coat and evade the host immune system. How the virus enters renal epithelial cells is uncertain because there is no evidence of renal epithelial expression of CD4 (the major HIV receptor in T helper cells) or the HIV-1 coreceptors, CXCR4 and CCR5. It is possible that HIV-1 infects renal epithelium via transcytosis from infiltrating lymphocytes.

Once the HIV-1 virus enters renal epithelium, it expresses viral genes that can cause cellular injury by inducing dysregulation of host genes. The HIV-1 genome contains a total of nine genes, including genes that encode structural proteins (*gag*, *pol*, *env*), regulatory proteins (*tat* and *rev*), and accessory proteins (*vif*, *vpr*, *vpu*, *nef*). The use of genetically engineered mice has identified several genes as particularly important in HIVAN pathogenesis, namely *nef* (which augments viral replication and infectivity) and *vpr* (which transports the HIV-1 preintegration complex into the nucleus and induces cell cycle arrest). In the podocyte, expression of *nef* activates signaling cascades that disrupt the actin cytoskeleton, causing foot process

HIV-ASSOCIATED NEPHROPATHY

(Continued)

effacement and failure to maintain the normal filtration barrier. Heavy glomerular proteinuria and nephrotic syndrome ensue. The infected podocytes revert to a more immature phenotype resembling that seen in proliferating podocytes during glomerular development. The inability of the podocyte to maintain its normal mature phenotype leads to cellular dedifferentiation, proliferation, and glomerular tuft collapse. The dysregulation of tubular epithelial cells by viral infection, compounded by the tubular injury caused by severe proteinuria, leads to tubular microcyst formation, interstitial fibrosis, and progressive renal failure. Tubular expression of *vpr* causes G2 cell cycle arrest and impairs cytokinesis of tubular epithelial cells, leading to increased chromosomal copy number. As a result, infected tubular epithelial cells appear hypertrophied with atypical enlarged nuclei.

Host factors are also critical to disease pathogenesis. The vast majority of patients with HIVAN are of African descent. Recently, a candidate gene has been linked to the development of HIVAN in this group: *APOL1*, encoding apolipoprotein L-1, located on human chromosome 22. An *APOL1* variant appears to have emerged in the African population through a broad evolutionary sweep by conferring selective advantage against infection by *Trypanosoma brucei rhodesiense*, a parasite that causes sleeping sickness. *APOL1* encodes a serum factor contained in high density lipoprotein particles that lyses the trypanosomal organism. The evolutionary selection of this genetic variant is analogous to the emergence of hemoglobin mutations that confer protection against malaria at the price of increased susceptibility to hemoglobinopathy and sickle cell anemia. In the case of *APOL1*, protection against trypanosomal infection comes at the cost of increased susceptibility to HIVAN and other forms of FSGS, although the renal cellular mechanisms are unknown. Like the mutations underlying sickle cell disease and trait, *APOL1*'s protective effect against infection is dominant (present in heterozygotes), whereas the association with host disease is recessive (occurring in homozygotes).

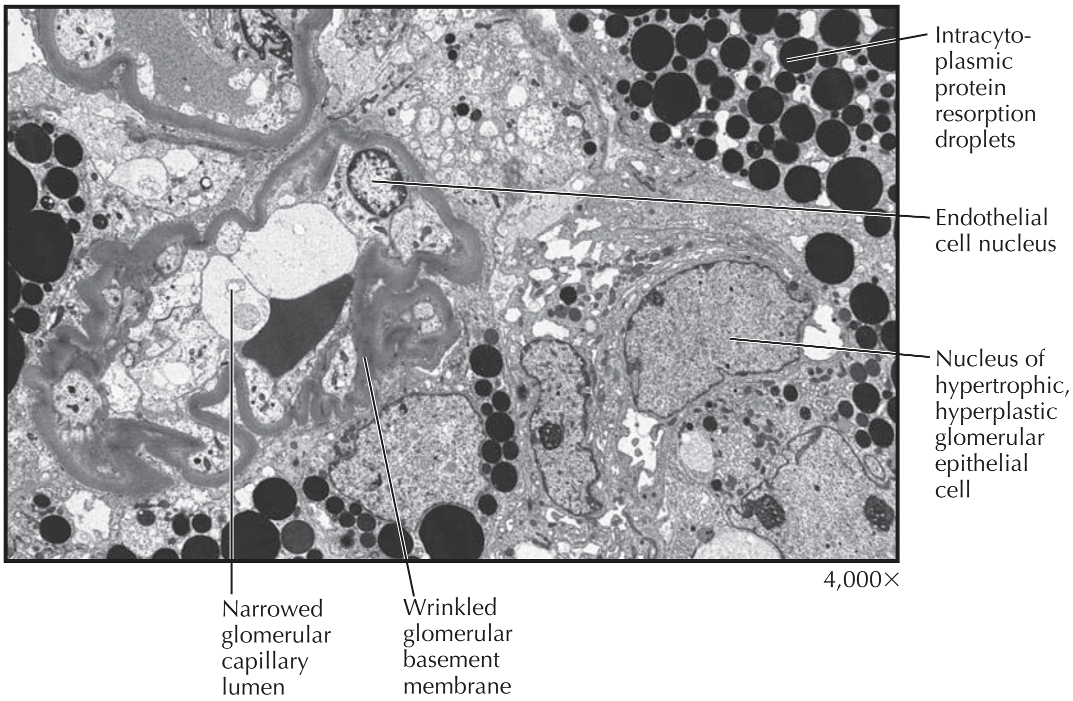
PRESENTATION AND DIAGNOSIS

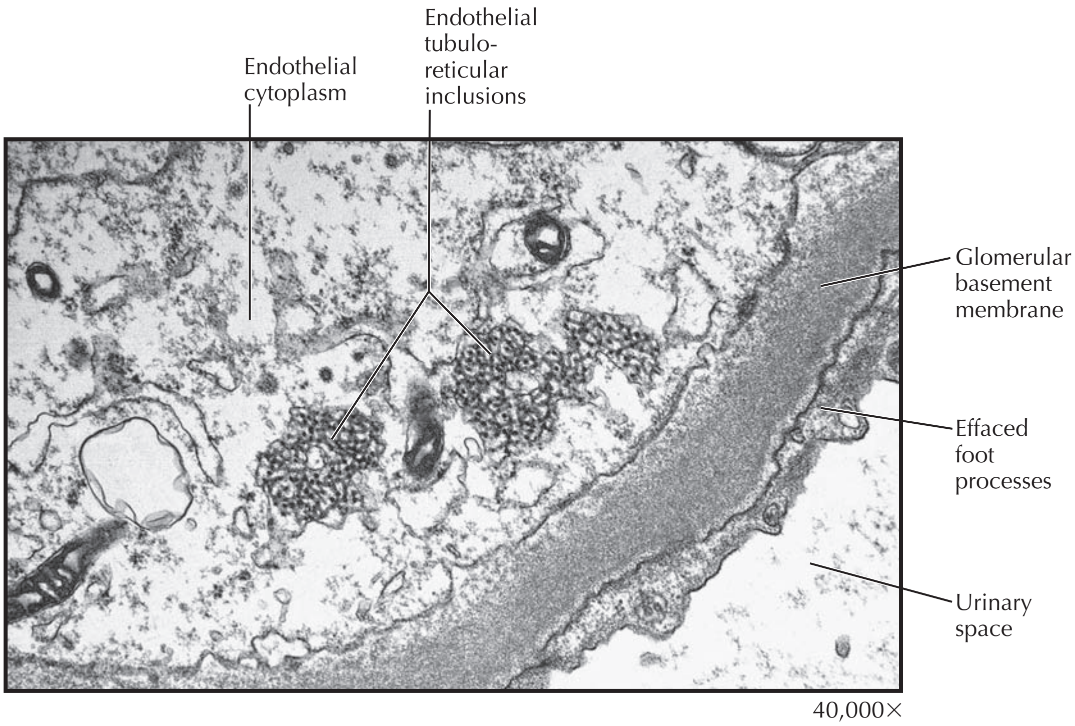
In the early years of the AIDS epidemic, before antiretroviral therapy, the classic clinical presentation of HIVAN was rapidly progressive renal failure accompanied by moderate to severe nephrotic-range proteinuria, bland urinary sediment, and the ultrasound findings of large, highly echogenic kidneys. Patients progressed to ESRD within several months.

Although some cases have been reported in the setting of asymptomatic HIV infection or acute HIV seroconversion, HIVAN is typically a complication of advanced HIV disease. Thus HIV-infected patients who develop nephrotic-range proteinuria and have a CD4 cell count less than 200 cells/mm^3 should be strongly suspected of having HIVAN. A renal biopsy is required to establish the diagnosis and exclude other causes of renal dysfunction and proteinuria, including numerous HIV-related glomerular diseases, non-HIV-related renal diseases, and medication nephrotoxicity. Other glomerular lesions encountered in the HIV-infected patient include thrombotic microangiopathy, immune complex-mediated glomerular disease (such as membranoproliferative or membranous glomerulonephritis related to coinfection with hepatitis C or hepatitis B viruses, acute postinfectious glomerulonephritis, lupus-like nephritis, and IgA nephropathy). These immune complex forms of glomerulonephritis are more common in HIV-infected Caucasians than African Americans. Other renal biopsy findings in the age of antiretroviral therapy include hypertensive arterionephrosclerosis and diabetic nephropathy.

In the acute phase, untreated HIVAN typically causes a dramatic pattern of collapsing FSGS. Glomerular capillary lumina are occluded by an implosive wrinkling and collapse of the glomerular basement membranes that is more often global than segmental. Tuft collapse is accompanied by prominent hypertrophy and hyperplasia of the overlying podocytes (visceral epithelial cells), which have enlarged; open vesicular nuclei with frequent nucleoli; and occasional mitotic figures. The podocyte cytoplasm is typically vacuolated, containing intracytoplasmic protein resorption (hyaline) droplets. Exuberant visceral and parietal epithelial cell proliferation can form pseudocrescents that obliterate the

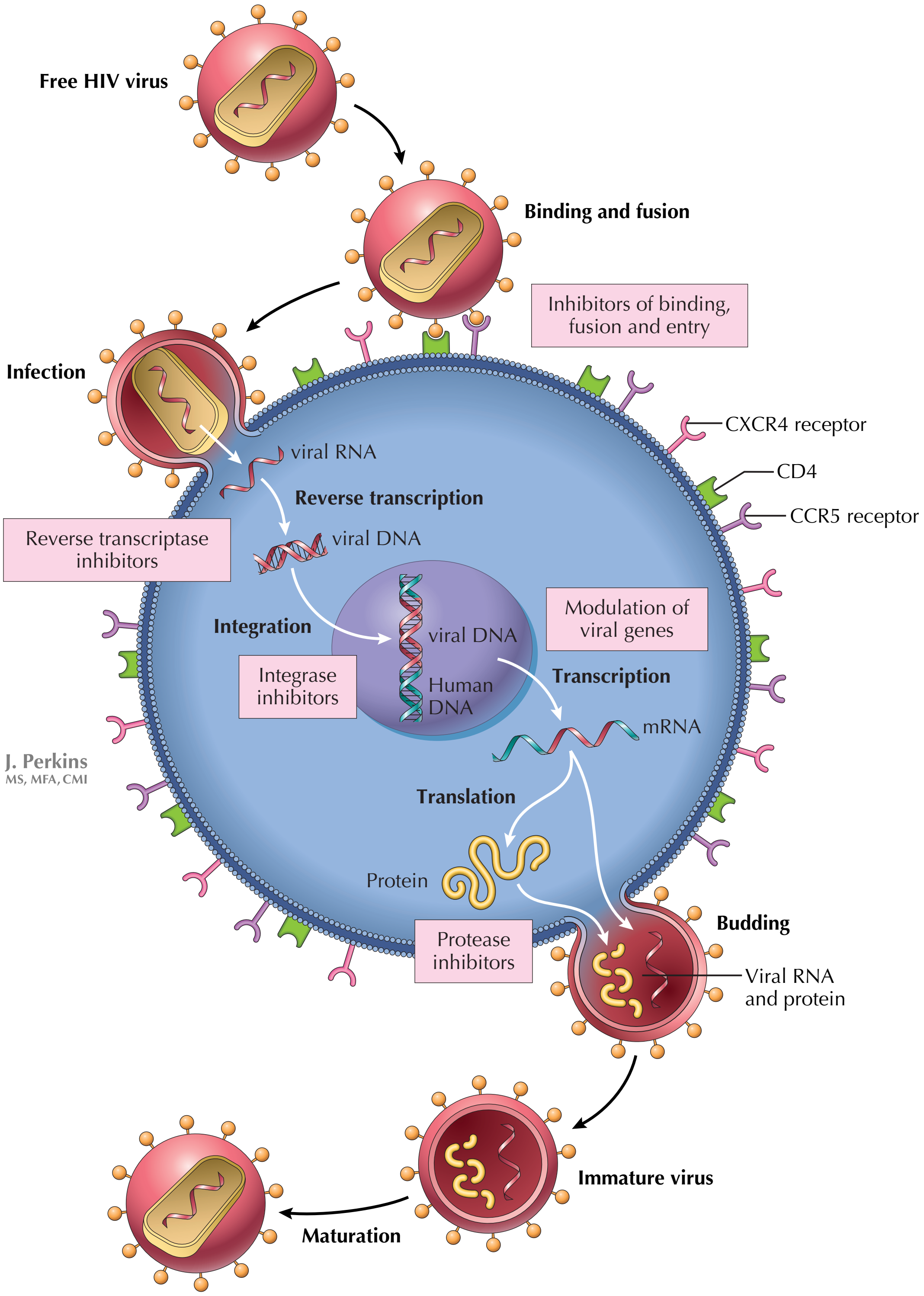
ELECTRON MICROSCOPY FINDINGS OF HIV-ASSOCIATED NEPHROPATHY


Intracytoplasmic protein resorption droplets
Endothelial cell nucleus
Nucleus of hypertrophic, hyperplastic glomerular epithelial cell
4,000×
Narrowed glomerular capillary lumen
Wrinkled glomerular basement membrane


Endothelial cytoplasm
Endothelial tubulo-reticular inclusions
Glomerular basement membrane
Effaced foot processes
Urinary space
40,000×

HIV-ASSOCIATED NEPHROPATHY
(Continued)

MECHANISMS OF INFECTION AND ANTIRETROVIRAL THERAPY



urinary space. Eventually, the glomerular tuft retracts into a tight, solidified ball crowned by enlarged, vacuolated visceral epithelial cells.

Tubulo-interstitial disease is an invariable component of HIVAN and often appears out of proportion to the degree of glomerular injury. In addition to tubular atrophy, interstitial fibrosis, edema, and inflammation, there are also widespread tubular degenerative and regenerative changes, including acute tubular epithelial injury and hypertrophy with enlarged hyperchromatic nuclei, prominent nucleoli, mitotic figures, and focal apoptosis. Distended tubules containing loose proteinaceous casts form tubular microcysts, which may be numerous and account for the enlarged appearance of the kidneys on radiographic imaging or gross examination.

By immunofluorescence, there are no immune complex type deposits. Segmental to global staining for IgM, C3, and less commonly C1 is frequently observed in the collapsing segments. These immune reactants are nonspecifically trapped in areas of sclerosis.

By electron microscopy, the glomerular capillaries are narrowed by wrinkling and retraction of the glomerular basement membranes. The overlying podocytes are markedly hypertrophied with severe foot process effacement, disruption of the actin cytoskeleton, focal cellular detachment, and intracytoplasmic protein resorption droplets. No typical immune type of electron dense deposits are observed. The glomerular endothelial cells contain characteristic tubulo-reticular inclusions, also known as “interferon footprints.” These 24 nm structures are located in dilated cisternae of smooth endoplasmic reticulum and constitute a marker of HIV infection that can be found in endothelial cells and lymphocytes throughout the body. Importantly, tubulo-reticular inclusions are not a specific feature of HIVAN and may be found in HIV-infected patients without nephropathy, as well as in patients with systemic lupus erythematosus, hepatitis C, or other viral infections. Endothelial tubulo-reticular inclusions have become less common in renal biopsies from patients with HIVAN who are receiving antiretroviral therapy, consistent with a treatment-induced reduction in viral burden and associated cytokine dysregulation.

A biopsy picture of collapsing glomerulopathy is not specific for HIVAN. Differential diagnosis of the collapsing variant of FSGS includes primary (idiopathic) FSGS; infections by viruses such as parvovirus B19, SV40 or CMV; erythrophagocytosis syndrome; interferon therapy; pamidronate toxicity; acute vasoocclusive injury; and rare familial forms.

TREATMENT

The introduction of combination antiretroviral therapy in 1996 was followed by a decline in the incidence of HIVAN and in the number of new cases of ESRD attributed to HIVAN in the United States. Some case reports demonstrated histologic improvement of the glomerular collapse and tubular injury on repeat renal biopsies following antiretroviral therapy, paralleling improvements in renal function and proteinuria. In addition, antiretroviral therapy has been found to delay the course of renal failure and prolong renal survival.

Recent guidelines consider HIVAN an indication for the initiation of antiretroviral therapy, irrespective of CD4 cell count. Highly active antiretroviral therapy typically includes combinations of drugs from several classes, including nucleoside and nucleotide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. Therapy with ACE inhibitors or angiotensin receptor blockers may be added to reduce proteinuria and slow disease progression. Corticosteroids have been used as adjunct therapy in patients with aggressive disease or severe interstitial inflammation. Patients with HIVAN approaching ESRD can be maintained on hemodialysis or peritoneal dialysis. Select patients with remote HIVAN and well-controlled HIV infection are potential candidates for kidney transplantation.

PROGNOSIS

The natural history of untreated HIVAN was once rapid progression to ESRD. At present, however, both proteinuria and renal function can stabilize following antiretroviral therapy, with relatively slow disease progression. Patients who develop HIVAN while on antiretroviral therapy often exhibit a milder form of FSGS that lacks collapsing features.

PREECLAMPSIA

In normal pregnancy, blood pressure declines in the first trimester because of a drop in peripheral vascular resistance, despite a marked increase in blood volume and cardiac output. Hypertension during pregnancy, defined as systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg, is a major complication associated with a mortality rate of nearly 20% worldwide. It may be due to:

- Chronic, preexisting hypertension
- Gestational hypertension, which occurs after 20 weeks of pregnancy in a previously normotensive woman
- Preeclampsia or eclampsia
- Preeclampsia superimposed on chronic hypertension

Preeclampsia, a severe complication that occurs in 5% of pregnancies, is defined as the development of proteinuria (>300 mg/24 hr) and hypertension after 20 weeks of gestation in a previously normotensive woman.

Preeclampsia superimposed on chronic hypertension is defined as the appearance of proteinuria after 20 weeks of gestation. If both hypertension and proteinuria exist before 20 weeks of gestation, preeclampsia is defined as a worsening of the hypertension to systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg or more after 20 weeks of gestation.

In most cases, preeclampsia occurs in the third trimester, although it may occur earlier in a patient with underlying renal disease. It is classified as either “mild” or “severe”; criteria for upstaging to severe preeclampsia are listed in the figure.

PATHOPHYSIOLOGY

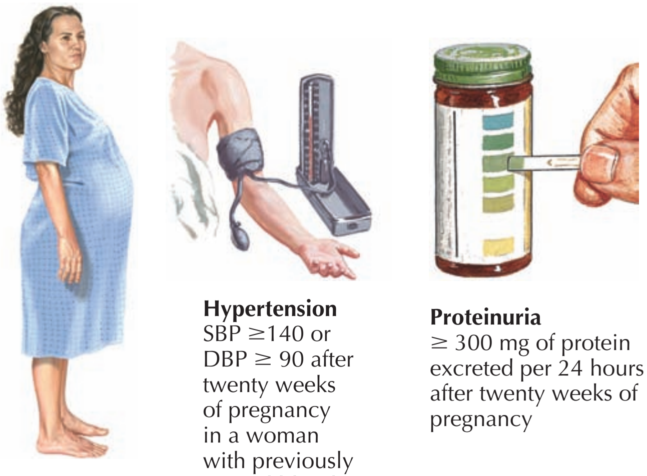
Despite intense research, the pathogenesis of preeclampsia remains poorly understood. Current evidence, however, suggests there is abnormal remodeling of the uterine spiral arteries, and that the resulting placental ischemia triggers release of antiangiogenic substances that increase blood pressure and cause diffuse endothelial dysfunction. In the glomerulus, endothelial dysfunction leads to proteinuria.

One of the factors that may mediate the connection between placental ischemia and preeclampsia is the soluble fms-like tyrosine kinase-1 receptor (sFlt1). Flt-1 is a membrane-bound receptor for VEGF and placental growth factor (PlGF). In response to ischemia, however, the placenta releases increased quantities of the soluble, unbound splice-variant sFlt-1, which scavenges circulating VEGF and PlGF without completing their normal signal cascades. The effective reduction in VEGF levels is associated with endothelial cell dysfunction and hypertension, since this factor normally induces endothelial nitric oxide. The dysfunctional endothelial cells may also contribute to the elevation in blood pressure by producing a smaller amount of vasodilatory prostaglandins.

Endothelial dysfunction is most prominent in the brain, liver, and kidney. In the kidney, the pathognomonic finding is glomerular endotheliosis, which consists of swollen glomerular endothelial cells and occluded, bloodless capillary lumina. It appears that the dysfunctional endothelial cells permit the passage of protein into the urine, since in contrast to many other proteinuric conditions, the podocytes and their foot processes often appear intact. Protein frequently accumulates in the subendothelial space, producing dense-appearing deposits.

CLINICAL DEFINITION AND POTENTIAL MECHANISM OF PATHOGENESIS OF PREECLAMPSIA

Clinical definition



Hypertension
SBP ≥140 or DBP ≥ 90 after twenty weeks of pregnancy in a woman with previously normal blood pressure

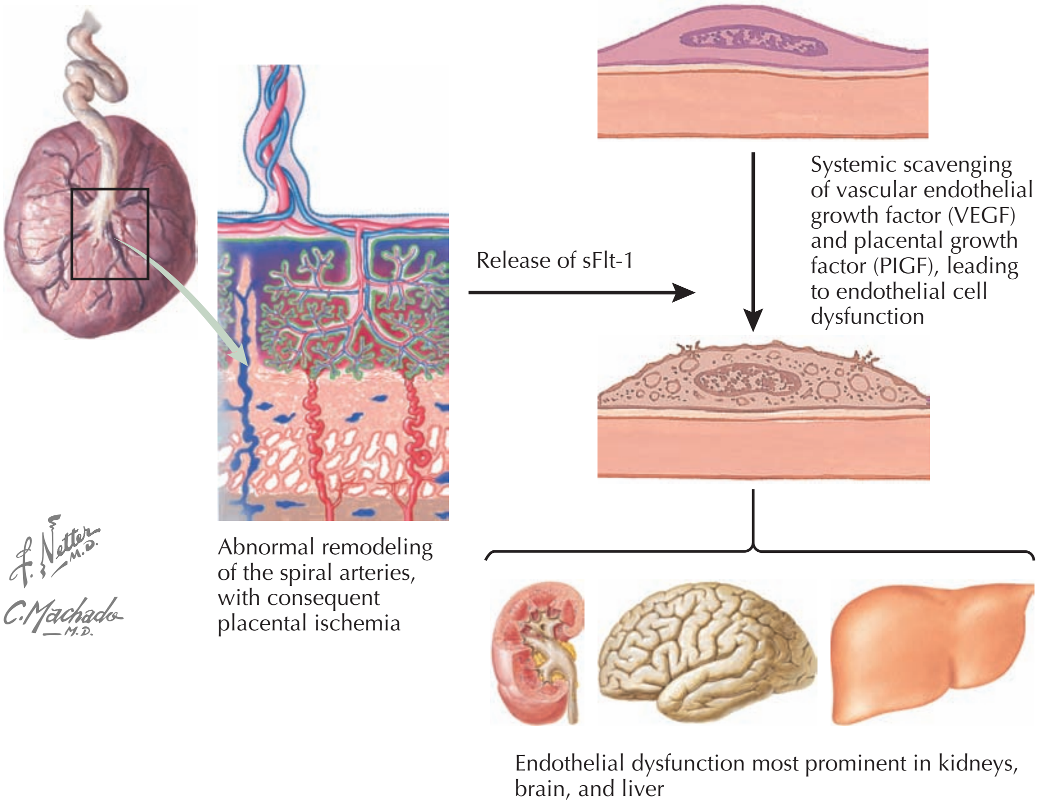
Proteinuria
≥ 300 mg of protein excreted per 24 hours after twenty weeks of pregnancy

Pre-eclampsia is diagnosed as “severe” if any of the following are also present:

- SBP ≥ 160 or DBP ≥110 on two occasions at least six hours apart while patient is on bed rest
- ≥ 5 g of protein excreted in urine per 24 hours or 3+ dipstick samples collected > 4 hours apart
- Oliguria (<500 mL of urine per 24 hours)
- Cerebral or visual disturbances
- Pulmonary edema, cyanosis
- Epigastric or right-upper quadrant pain
- Transaminase elevation (>2× normal levels)
- Thrombocytopenia
- Fetal growth restriction

Adapted from Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin No. 33. American College of Obstetricians and Gynecologists. Obstet Gynecol 2002;99:159-167.

Potential mechanism of disease pathogenesis


Release of sFlt-1
Systemic scavenging of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), leading to endothelial cell dysfunction
Abnormal remodeling of the spiral arteries, with consequent placental ischemia
Endothelial dysfunction most prominent in kidneys, brain, and liver

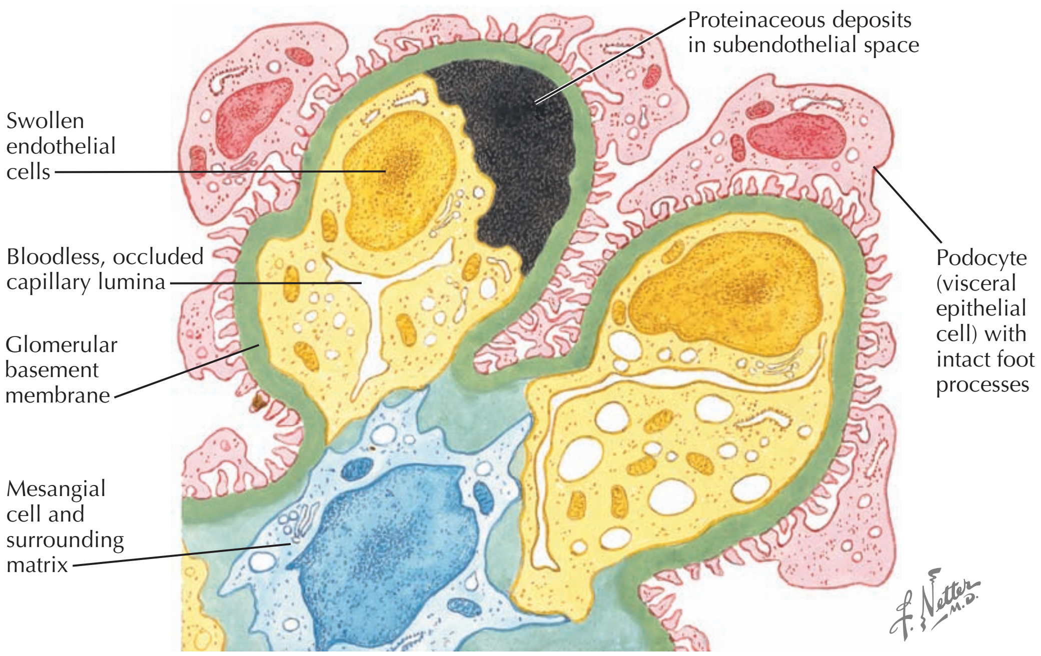
The importance of sFlt-1 in the pathogenesis of preeclampsia is underscored by the fact that administration of this factor to mice produces hypertension, proteinuria, and glomerular endotheliosis. Not all women with elevated sFlt-1 levels, however, develop preeclampsia, and not all women with preeclampsia have elevated sFlt-1 levels. Thus other factors involved in precipitating preeclampsia continue to be investigated.

The renin-angiotensin-aldosterone system, for example, may also play a role in the pathogenesis of preeclampsia. In normal pregnancy, this axis is stimulated to maintain blood pressure. In preeclampsia, however, there is an exaggerated response to angiotensin II. There are several possible explanations for this difference. First, placental ischemia leads to increased expression of bradykinin B2 receptors, which form heterodimers with the AT1 angiotensin II receptor. These heterodimers are more sensitive to angiotensin II than normal AT1 receptors. In addition, preeclampsia is associated with increased levels of agonistic anti-AT1 antibodies for unknown reasons.

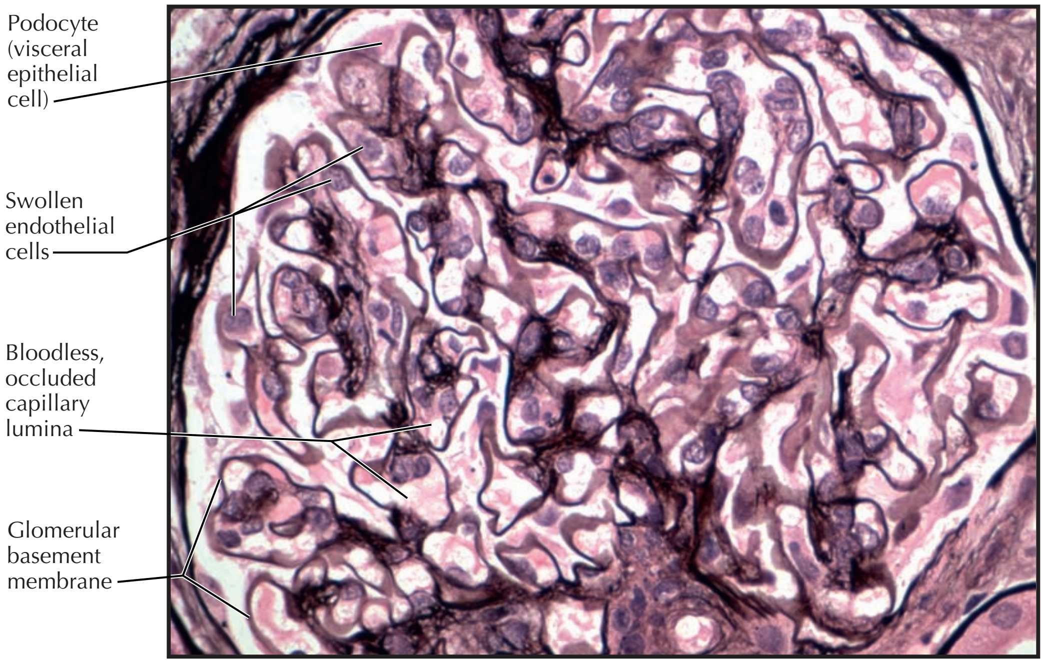
The events leading to abnormal remodeling of the placental vasculature are also unclear. Recent work, however, has focused attention on the enzyme

PREECLAMPSIA *(Continued)*

Renal Pathology of Preeclampsia


Proteinaceous deposits in subendothelial space
Swollen endothelial cells
Bloodless, occluded capillary lumina
Glomerular basement membrane
Mesangial cell and surrounding matrix
Podocyte (visceral epithelial cell) with intact foot processes
F. Netter M.D.

Light microscopy findings


Podocyte (visceral epithelial cell)
Swollen endothelial cells
Bloodless, occluded capillary lumina
Glomerular basement membrane

Silver stain, 400×

catechol-O-methyltransferase (COMT), which produces 2-methoxyestradiol (2-ME), a natural metabolite of estradiol that is elevated in the third trimester. Both COMT and 2-ME have been shown to be deficient in patients with severe preeclampsia. Pregnant mice that lack COMT are deficient in 2-ME and develop placental hypoxia, high sFlt1 levels, and symptoms of preeclampsia that improve when 2-ME is replenished.

RISK FACTORS

Genetic and environmental factors increase the risk for preeclampsia. A positive family history has been shown to increase the risk; indeed, the mouse model of COMT and 2-ME deficiency further emphasizes the role of genetics. Other factors associated with increased risk include prior preeclampsia, advanced maternal age, nulliparity, and twin gestation.

In addition, pregnant women with preexisting hypertension, chronic kidney disease, diabetes mellitus, and obesity are at greater risk. It is possible that these conditions sensitize the endothelium to the antiangiogenic effects of factors such as s-Flt1.

PRESENTATION AND DIAGNOSIS

In most cases, preeclampsia is detected during routine blood pressure screening and urine dipstick. Because of primary renal retention of salt and water, patients may have edema and rapid weight gain. A 24-hour urine collection or spot urine protein : creatinine ratio should be performed to monitor the degree of proteinuria. Serum creatinine concentration is normally low in pregnancy due to hemodilution and may begin to rise with preeclampsia. Serum uric acid may be elevated because of diminished renal clearance. Finally, there may be abnormal liver function tests and evidence of hemolysis on the complete blood count, which suggests HELLP syndrome. The presence of headache and/or visual changes should alert the physician of possible progression to eclampsia.

COMPLICATIONS: HELLP SYNDROME AND ECLAMPSIA

The complications of preeclampsia can be severe. HELLP syndrome affects up to 20% of patients with severe preeclampsia, and it is characterized by *HE*molysis, abnormally elevated *L*iver function tests, and *L*ow *P*latelets. This complication appears to reflect severe endothelial dysfunction in the liver, which leads to platelet aggregation and thrombotic occlusion of the hepatic sinusoids, resulting in transaminitis. Red cells are sheared while passing through the narrowed vessels, resulting in microangiopathic hemolytic anemia. Stretching of the Glisson capsule often leads to right upper quadrant pain, nausea, and vomiting, which are the major clinical symptoms. Less frequently, jaundice may occur. Major complications include subcapsular hepatic hematoma formation, placental abruption, retinal detachment, acute kidney injury, pulmonary edema, and disseminated intravascular coagulation.

Eclampsia affects 2% of patients with severe preeclampsia, and it is defined as the occurrence of seizures in the setting of preeclampsia. This complication appears to reflect severe endothelial dysfunction in the brain, which leads to cerebral edema and formation of microthrombi. Early warning signs include headaches and visual changes; indeed, the Greek word *eklampsis* means “sudden flashing” and refers to these visual signs. Cerebral hemorrhage is a potentially fatal complication.

Both HELLP syndrome and eclampsia are associated with a dramatic increase in morbidity and mortality for both mother and fetus.

TREATMENT

Delivery is the definitive treatment for preeclampsia and should be promptly undertaken in women past 37 weeks of gestation. If the fetus is not yet at term, however, patients with mild preeclampsia may undergo careful monitoring to ensure rapid diagnosis of fetal distress and/or maternal complications. Reliable patients can be managed with frequent checks on an outpatient basis; however, patients often need to be hospitalized for careful monitoring, especially if there is any evidence of disease progression.

Intravenous magnesium sulfate is used to treat eclamptic seizures and should be given to all patients with preeclampsia and HELLP syndrome as prophylaxis. Although there is no widely accepted regimen, it is typically given intrapartum and continued for 1 to 2 days postpartum.

PREECLAMPSIA *(Continued)*

In all pregnant women, whether there is evidence of preeclampsia or not, antihypertensive medications are indicated if systolic blood pressure is ≥150-160 mm Hg, diastolic pressure is ≥100-110 mm Hg, or if there is evidence of end-organ damage. The thresholds are higher than in nonpregnant women because the goal is to prevent severe complications in the mother during the pregnancy without harming the fetus, rather than preventing long-term cardiovascular complications as in nonpregnant patients. Moreover, if there is a sustained decline in blood pressure, the fetus may experience distress or growth retardation.

Most antihypertensive agents are safe for use during pregnancy, with the significant exception of those that block the renin-angiotensin system. Angiotensin II plays an important role in nephrogenesis, and the use of ACE inhibitors or angiotensin receptor blockers (ARBs) may cause profound abnormalities in fetal renal development.

Alpha-methyldopa is the drug of choice for chronic hypertension in pregnancy because it has the best long-term safety profile. Labetalol and other β-blockers have been used successfully during pregnancy, and intravenous labetalol is considered the drug of choice for severe hypertension in pregnancy. Although hydralazine has been used for many years, recent data suggest that its safety profile is inferior to that of labetalol.

Calcium channel blockers are effective, although blood pressure may fall precipitously if these agents are administered along with magnesium sulfate. Diuretics are generally not used because they restrict the normal volume expansion associated with pregnancy and may reduce uteroplacental blood flow.

If there is progression to severe preeclampsia, immediate delivery is often required, although some patients who are not yet at term may be candidates for cautious expectant management. Further progression to HELLP syndrome or eclampsia, however, mandates delivery. For pregnancies at less than 34 weeks of gestation, glucocorticoids may be given in advance to promote fetal lung maturation.

PROGNOSIS

Preeclampsia typically resolves within several days postpartum, but symptoms can sometimes persist for weeks or more. Patients should be carefully monitored for the duration of their postpartum hospitalization and may require continued antihypertensive therapy for several weeks after discharge.

Women who experience preeclampsia are at increased risk for recurrence in subsequent pregnancies. In general, women with more severe disease are at greater risk for recurrence. These women are also at elevated risk for developing metabolic syndrome and cardiovascular disease later in life, which may reflect either underlying endothelial dysfunction or permanent cardiovascular sequelae associated with preeclampsia. There is a slight increase in the risk of end-stage renal disease compared to the rest of the population, although the absolute risk is still low.

PREVENTION

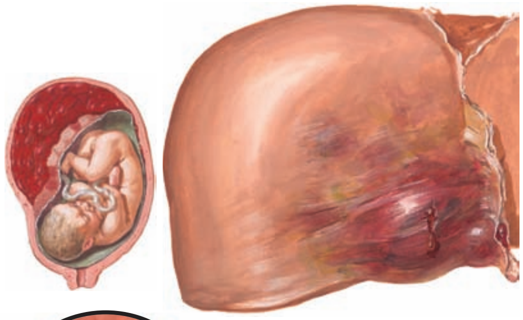
A number of therapies have been used in attempts to prevent or slow the progression of preeclampsia, so far with little success. The drug with the most data is aspirin, which may exert its benefit by altering the abnormal prostaglandin-thromboxane ratios associated with endothelial dysfunction. Although many trials have shown no benefit of aspirin, a recent meta-analysis suggested that if started before 16 weeks of gestation, it may diminish the incidence and/or severity of preeclampsia in high-risk patients. Agents such as vitamin D, antioxidants, and sildenafil have been examined but have so far failed to show any protective effect.

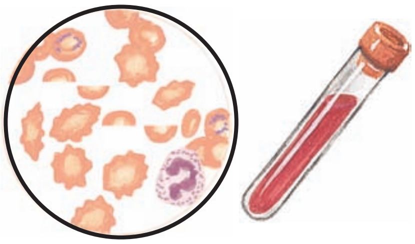
Several tests to identify the patients at highest risk for preeclampsia have been investigated, including uterine artery Doppler ultrasound and measurement of VEGF, sFlt-1, and other angiogenic factors in blood and urine. Although these tests show some promise, at present they have limited usefulness because there is no way to prevent the emergence or progression of preeclampsia. Thus early detection through frequent screening of blood pressure and urine protein is of utmost importance, especially in high-risk patients. Educating patients about symptoms that may be potential warning signs is also valuable.

HELLP Syndrome and Eclampsia

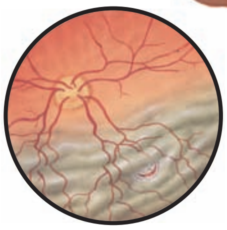
HELLP Syndrome (Hemolysis, Abnormal Liver Function Tests, Low Platelets)

Clinical symptoms
Nausea, vomiting
Right upper quadrant pain
Jaundice





Laboratory findings
- Hemolysis (with schistocytes seen on peripheral smear)
- Elevated liver function tests
- Low platelet count

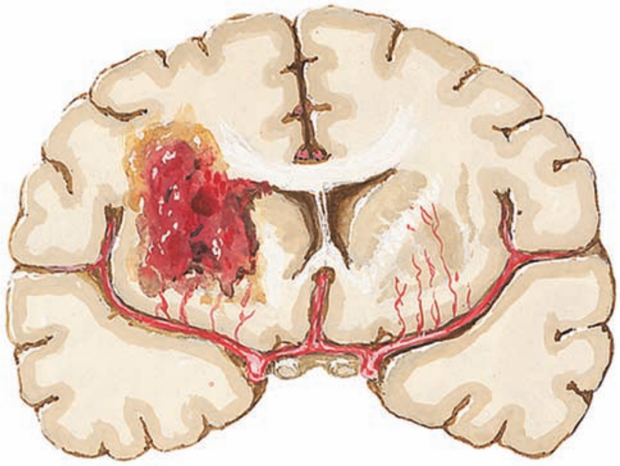


Complications
- Placental abruption
- Hepatic subcapsular hematoma
- Retinal detachment
- Acute kidney injury
- Pulmonary edema
- Disseminated intravascular coagulation (DIC)

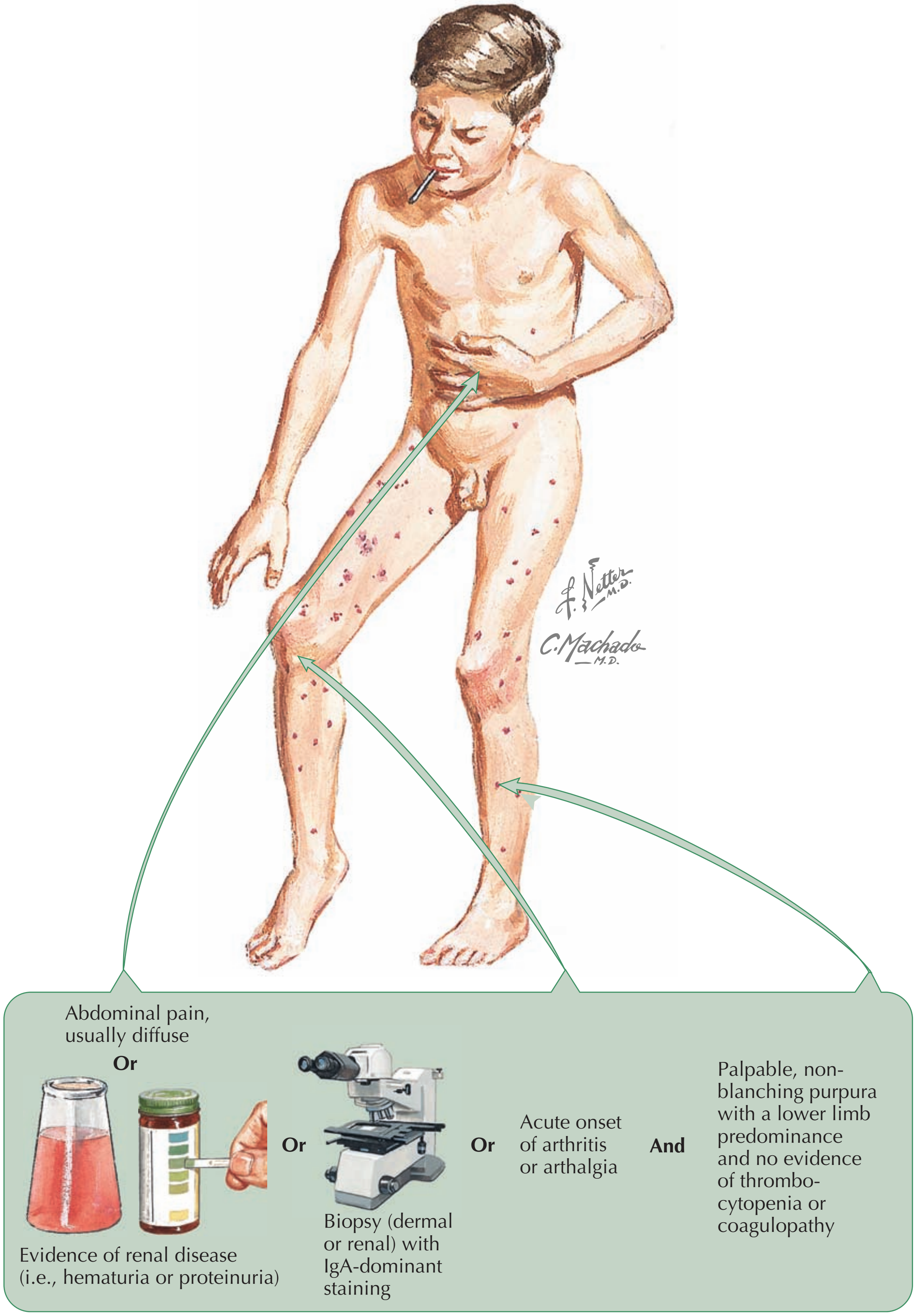
Eclampsia

Clinical symptoms
- Generalized, tonic-clonic seizure
- Early symptoms may include:
  Blurred vision
  Severe frontal or occipital headache
  Altered mental status

Complications
- Cerebral hemorrhage



DIAGNOSTIC CRITERIA OF HENOCH-SCHÖNLEIN PURPURA


F. Netter M.D.
C. Machado M.D.
Abdominal pain, usually diffuse
Or
Evidence of renal disease (i.e., hematuria or proteinuria)
Or
Biopsy (dermal or renal) with IgA-dominant staining
Or
Acute onset of arthritis or arthralgia
And
Palpable, non-blanching purpura with a lower limb predominance and no evidence of thrombocytopenia or coagulopathy

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis that can affect the skin, joints, connective tissue, gastrointestinal tract, and kidneys. It usually affects children who are between the ages of 3 and 15, among whom the incidence is approximately 10 to 20 per 100,000/year. Less often, HSP may also affect adults, generally with more severe symptoms.

HSP occurs secondary to deposition of IgA1-dominant immune complexes in arterioles, capillaries, and venules. The pathology of the renal lesion is indistinguishable from that seen in IgA nephropathy; indeed, many consider the two conditions to be on the same pathogenetic spectrum, with HSP distinguished by the presence of extrarenal involvement.

PATHOPHYSIOLOGY

The pathogenesis of HSP is largely unknown. Systemic deposition of IgA appears to activate the alternative complement pathway. As in IgA nephropathy (see Plate 4-16), abnormal underglycosylation of the IgA1 hinge region appears to play a role in promoting abnormal deposition, although the exact mechanisms remain poorly understood. As in IgA nephropathy, the renal disease is associated with IgA binding of mesangial cells and subsequent inflammation.

IgA1 antibodies are produced by peripheral B lymphocytes, but the reason for their abnormal production is unclear. Case reports have noted that HSP occurs after antecedent infections with measles, hepatitis, varicella, group A *Streptococcus*, and tuberculosis, as well as after vaccinations and insect bites. Although these findings suggest that abnormal immune responses to common pathogens may play a role, such an association remains speculative.

PRESENTATION AND DIAGNOSIS

The major features include palpable, nonblanching purpura (often on the lower extremities), nonerosive oligoarthritis, renal disease, and gastrointestinal disease. Most patients, however, do not exhibit all four of these components.

The renal disease can include microscopic or macroscopic hematuria, proteinuria, renal insufficiency, or a combination. Especially in adults, the proteinuria may be severe enough to cause signs and symptoms of the nephrotic syndrome, and acute kidney injury may also occur. The gastrointestinal disease, which occurs secondary to submucosal edema and hemorrhage, may be limited to pain and vomiting. Some patients, however, may experience more significant complications, such as frank gastrointestinal hemorrhage or intussusception. Less common systemic manifestations include scrotal pain or swelling, as well as central nervous system disease (i.e., headache, seizures).

The major presenting symptoms tend to be palpable purpura and arthritis, with gastrointestinal and renal involvement developing in some patients over subsequent days and weeks. This sequence, however, is not universal; in 20% to 40% of patients, for example, gastrointestinal symptoms may precede the rash. Likewise, 20% to 50% may have renal involvement at the initial presentation. Urinalysis may be remarkable for dysmorphic red blood cells, red blood cell casts, and protein. Laboratory analysis of serum is generally unremarkable, although some patients may have evidence of mild renal dysfunction. In addition, those with more severe proteinuria may be found to have hypoalbuminemia and hypercholesterolemia as parts of the nephrotic syndrome. Complement levels are generally normal. Frank gastrointestinal bleeding may cause anemia, which should be assessed using guaiac testing of stool. Platelet counts and assays of clotting function should be normal, which can be used to exclude other causes of purpura. IgA levels are elevated in about half of patients but are neither sensitive nor specific for the diagnosis of HSP.

According to current diagnostic criteria, a patient is considered to have HSP if purpura or petechiae have a lower limb predominance, there is no evidence of thrombocytopenia or coagulopathy, and any one of

HENOCH-SCHÖNLEIN PURPURA

(Continued)

following four criteria are met: (1) abdominal pain; (2) arthritis or arthralgia; (3) renal involvement (hematuria, proteinuria); and (4) histopathology showing IgA dominant or codominant deposition. The diagnosis can usually be established based on clinical indicators. When the diagnosis is uncertain but the level of suspicion is high, a skin biopsy may be performed, which classically reveals a leukocytoclastic vasculitis with IgA-dominant deposition seen on immunofluorescence.

In patients with marked renal insufficiency, a renal biopsy may be performed to determine the extent of disease and assess for the presence of rare but serious manifestations, such as crescentic glomerulonephritis (see Plate 4-25). The renal pathologic findings are nearly identical to those seen in IgA nephropathy (see Plate 4-17). Using light microscopy, mesangial hypercellularity is often the major feature. In more severe cases, there may be variable amounts of endocapillary leukocyte infiltration and cellular crescent formation, with the latter portending a poorer prognosis. In the most severe cases, the glomerular basement membrane may appear "split," as in membranoproliferative glomerulonephritis (see Plate 4-22).

Immunofluorescence reveals dominant or codominant granular staining for IgA in the mesangium and sometimes the capillary wall. Staining for IgG and IgM may also be positive but with less intensity. The immune deposits often colocalize with C3 but only rarely with C1q. Finally, electron microscopy reveals electron dense deposits that correspond with the pattern of immune complex deposition seen on immunofluorescence.

TREATMENT

Most patients experience self-limited disease that resolves within weeks to months. During this time, treatment is mostly supportive. Nonsteroidal antiinflammatory drugs may be given for relief of arthritis. These do not appear to substantially increase the risk of gastrointestinal hemorrhage but may be avoided in patients with existing hemorrhage or with poor renal function (because of their effect on tubuloglomerular feedback [see Plate 3-18]).

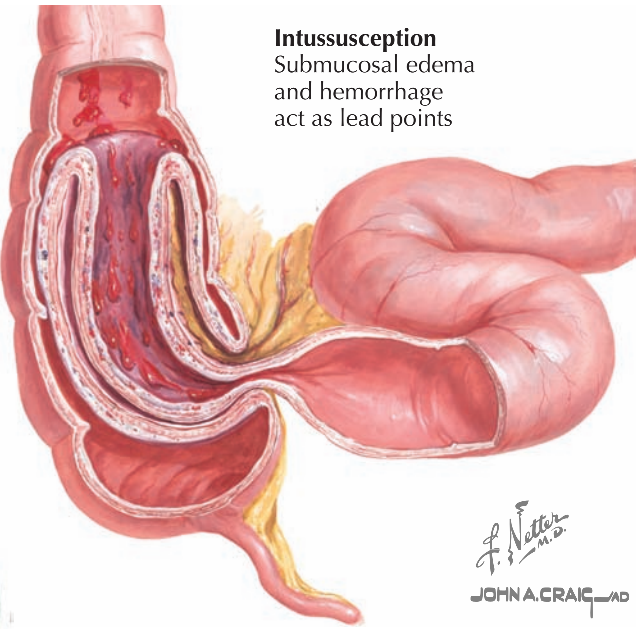
Unfortunately, there is a paucity of controlled trials regarding the treatment of severe HSP. There is some evidence that corticosteroids may improve gastrointestinal symptoms and arthritis. There is no evidence, however, that corticosteroids, cyclophosphamide, or any other agents are effective in the treatment of HSP-associated renal disease. Such agents are often given to patients with more severe disease seen on renal biopsy, such as cellular crescents, but their efficacy remains anecdotal. Plasmapheresis has also been attempted, with limited data indicating a beneficial effect.

PROGNOSIS

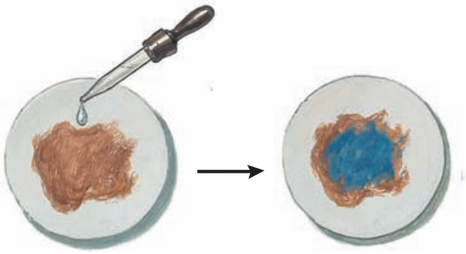
After the initial episode resolves, about one third experience bouts of disease recurrence, which are usually mild and occur during the first several months after presentation. Patients should thus receive careful follow-up during this period.

Additional Clinical Features of Henoch-Schönlein Purpura

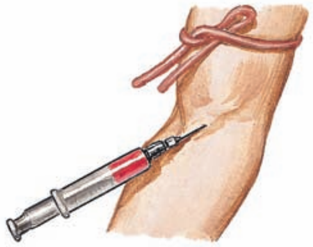
Vomiting



Intussusception Submucosal edema and hemorrhage act as lead points



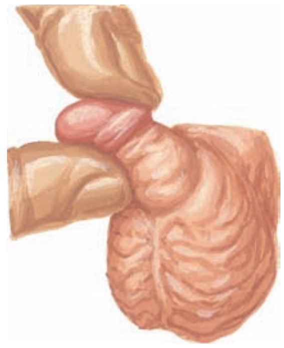
Gastrointestinal bleeding Occult (as seen on Guaiac testing) or frank



Hypoalbuminemia, if proteinuria is severe enough to cause nephrotic syndrome

Acute kidney injury, with rise in serum creatinine concentration

Edema, especially if proteinuria is severe enough to cause nephrotic syndrome



Scrotal pain or swelling

CNS symptoms, including headache and seizures

Most children have normal long-term renal function, with a small fraction experiencing persistent sediment abnormalities and even fewer experiencing renal insufficiency. In contrast, adults appear to have a worse renal prognosis, with a large series finding that 15% experienced ongoing moderate insufficiency, 13% developed advanced chronic kidney disease, and 10% progressed to ESRD. Worse prognoses are more likely in those who develop more severe renal symptoms and are found to have markers of more significant inflammation, such as cellular crescents, on renal biopsy.

Renal transplantation can be performed on those who have progressed to ESRD. Disease recurrence, however, occurs in up to 25% of patients at 5 years. Although overall graft and patient survival are similar, recurrence can be associated with graft loss, especially in patients with necrotizing or crescentic lesions in their native kidneys.

FABRY DISEASE

Fabry disease is a lysosomal storage disorder in which α-galactosidase A (α-Gal A), a lysosomal hydrolase, becomes mutated and dysfunctional. As a result its substrate, globotriaosylceramide (Gb3), accumulates within cells and causes disease involving multiple organ systems.

The gene encoding α-Gal A is located on the X-chromosome, and thus mutations are inherited in an X-linked manner. The estimated incidence is 1 in 40,000 males. Disease may also occur in female carriers, especially if X-inactivation (also known as lyonization) is skewed so that the mutant allele is more heavily expressed.

Renal complications usually begin in early adulthood and affect approximately half of patients by their fourth decade. Virtually all patients who survive into their sixth decade develop end-stage renal disease.

PATHOPHYSIOLOGY

In the kidney, Gb3 accumulation primarily affects podocytes (visceral epithelial cells), distal tubular cells, and vascular endothelium. The major symptoms that result are proteinuria, isosthenuria, and progressive renal insufficiency.

In the skin, Gb3 accumulation in dermal endothelial cells leads to dark red macules or papules—known as angiokeratomas—on the trunk, genitalia, thighs, and buttocks. In the eyes, Gb3 accumulation often causes clinically silent corneal opacities. In the nervous system, Gb3 accumulation can lead to painful paresthesia that is exacerbated by exercise and extreme temperatures.

In the cerebral vasculature, Gb3 accumulates in vascular smooth muscle and endothelial cells, where it is hypothesized to cause a local increase in leukocyte activation that can lead to thrombosis. Indeed, patients have an especially high risk of stroke, usually starting in their third decade.

In the heart, Gb3 accumulation causes left ventricular hypertrophy, arrhythmias, and valvular regurgitation. The mechanism underlying left ventricular hypertrophy is unclear, because the direct accumulation of Gb3 within cardiac myocytes appears to be responsible for only a small portion (approximately 1%) of the overall increase in cardiac mass. Meanwhile, arrhythmias and regurgitation reflect Gb3 deposition within the cardiac conduction system and valves, respectively.

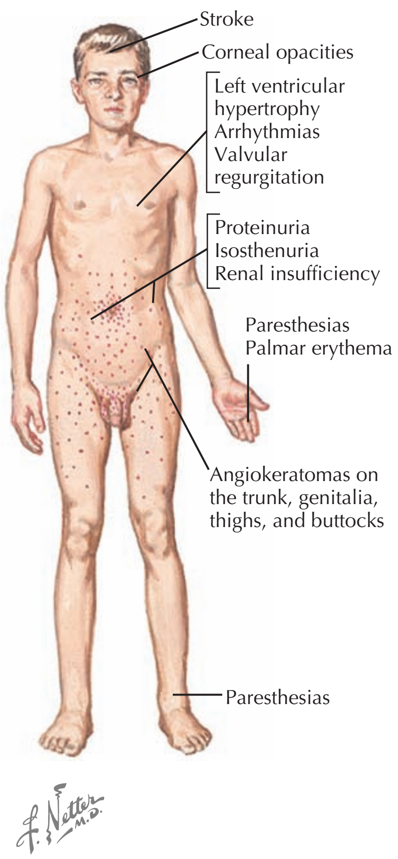
PRESENTATION AND DIAGNOSIS

Most patients begin to experience some of the previous symptoms during childhood. The diagnosis of Fabry disease should be suspected in the setting of a positive family history and progressive multisystem disease. Given the myriad nonspecific clinical symptoms, however, a variety of other conditions (often rheumatologic) are often first proposed instead, frequently delaying the correct diagnosis. Most males are diagnosed in childhood or puberty. Female carriers may be diagnosed later in life, depending on the severity of their clinical manifestations.

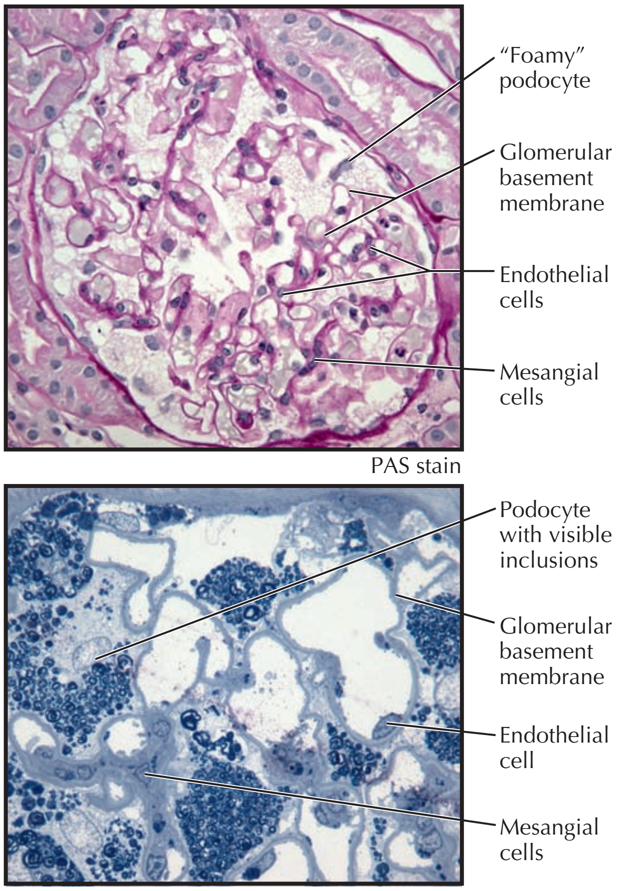
In males, the diagnosis can be confirmed by measuring α-Gal A enzyme activity within leukocytes. In female carriers, who retain a functional copy of α-Gal A, this test is less sensitive. Genetic sequencing can be performed to identify female carriers and screen families of affected individuals.

Before diagnosis, renal manifestations sometimes prompt renal biopsy. The classic findings using light microscopy include enlarged podocytes with abundant foamy cytoplasm due to the accumulation of lipid in lysosomes. Electron microscopy reveals enlarged lysosomes with a distinctive "zebra body" or "myelin figure" appearance secondary to the accumulation of Gb3. These abnormal lysosomes are seen in podocytes, endothelial cells, smooth muscle cells, and tubular epithelial cells. Zebra bodies, however, are not pathognomonic for Fabry disease because they are a relatively common feature in lysosomal storage disorders in general, as well as in other forms of phospholipidoses. In addition, they are seen in certain types of drug-related nephrotoxicity. Thus care must be taken to correlate clinical and pathologic findings.

Clinical features


Stroke
Corneal opacities
Left ventricular hypertrophy
Arrhythmias
Valvular regurgitation
Proteinuria
Isosthenuria
Renal insufficiency
Paresthesias
Palmar erythema
Angiokeratomas on the trunk, genitalia, thighs, and buttocks
Paresthesias

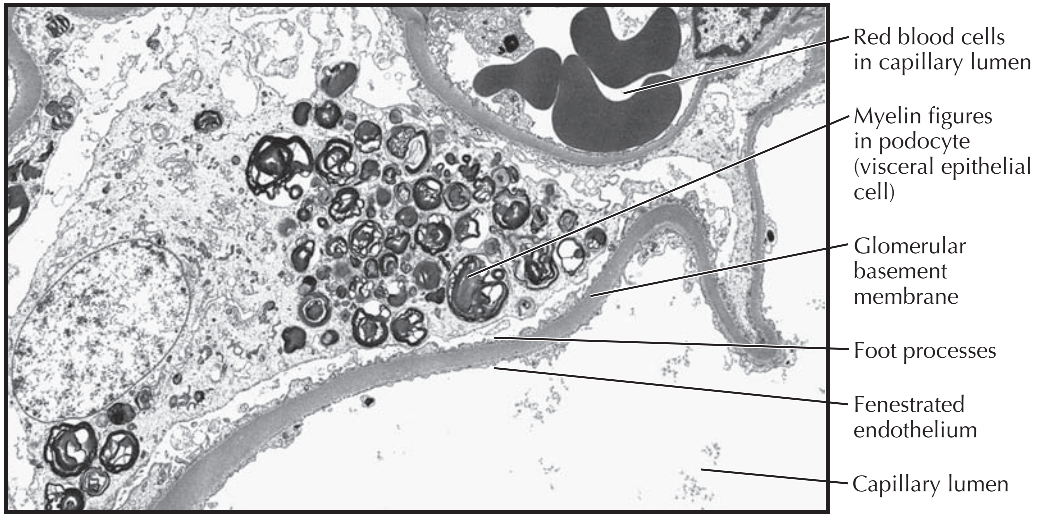
Light microscopy findings


"Foamy" podocyte
Glomerular basement membrane
Endothelial cells
Mesangial cells
Podocyte with visible inclusions
Glomerular basement membrane
Endothelial cell
Mesangial cells

PAS stain

Toluidine blue stain

Electron microscopy findings


Red blood cells in capillary lumen
Myelin figures in podocyte (visceral epithelial cell)
Glomerular basement membrane
Foot processes
Fenestrated endothelium
Capillary lumen

4000×

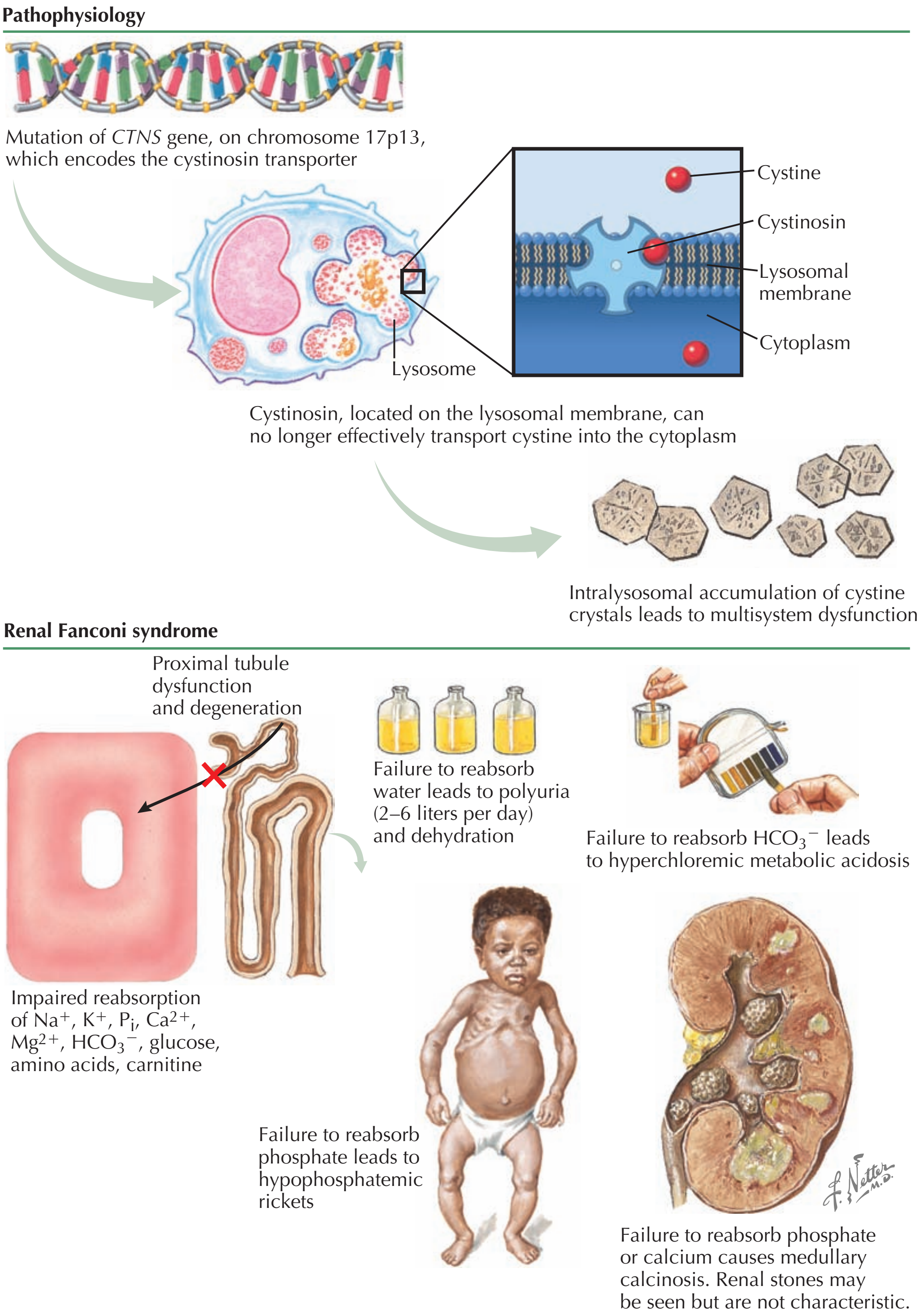
TREATMENT

Recombinant human α-Gal A can be given by intravenous infusion to replace the missing enzyme. It appears to both slow the progression of renal disease and decrease neuropathic pain. Its ability to prevent or reverse cardiac and cerebrovascular manifestations, however, is not well established.

Males with Fabry disease have a decreased life expectancy. Because of the numerous renal, cardiac, and neurologic complications, few live past the age of 60. The effect of enzyme replacement on mortality is currently unknown.

CYSTINOSIS

PATHOPHYSIOLOGY AND THE RENAL FANCONI SYNDROME



Pathophysiology

Mutation of *CTNS* gene, on chromosome 17p13, which encodes the cystinosin transporter

Cystinosin, located on the lysosomal membrane, can no longer effectively transport cystine into the cytoplasm

Intralysosomal accumulation of cystine crystals leads to multisystem dysfunction

Renal Fanconi syndrome

Proximal tubule dysfunction and degeneration

Impaired reabsorption of Na^+, K^+, P_i, Ca^{2+}, Mg^{2+}, HCO_3^-, glucose, amino acids, carnitine

Failure to reabsorb water leads to polyuria (2–6 liters per day) and dehydration

Failure to reabsorb HCO_3^- leads to hyperchloremic metabolic acidosis

Failure to reabsorb phosphate leads to hypophosphatemic rickets

Failure to reabsorb phosphate or calcium causes medullary calcinosis. Renal stones may be seen but are not characteristic.

Cystinosis is a multisystemic, autosomal recessive disorder of lysosomal transport that results in intracellular accumulation of the amino acid cystine, which leads to cellular dysfunction and death. The incidence of this disease is estimated at 1 per 100,000 to 200,000 live births, and it occurs in all ethnic groups.

There are three forms of cystinosis. The most severe is nephropathic (infantile) cystinosis (NC), which accounts for 95% of cases. Intermediate (juvenile) cystinosis has a later onset of renal complications, whereas ocular (non-nephropathic) cystinosis generally causes only corneal crystals.

NC first presents in early infancy with generalized renal proximal tubular dysfunction. Untreated, it progresses to chronic kidney disease in the first decade of life. In the past, an affected child's lifespan was limited to 10 years; however, with the emergence of kidney transplantation and effective medical treatment (including cystine-depleting agents), patients can now expect a reasonably normal quality of life for several decades.

PATHOPHYSIOLOGY

Patients with cystinosis have mutations in the *CTNS* gene, located on chromosome 17p13. This gene encodes cystinosin, a lysosomal membrane transport protein that contains 367 amino acids and 7 transmembrane domains. *CTNS* mutations account for all types of cystinosis, and more severe mutations are associated with the NC form. Approximately 100 different *CTNS* mutations have been identified; the most common is a 57,257 base pair deletion, which is present in the homozygous or heterozygous state in about 76% of NC patients of northern European origin.

Functional cystinosin deficiency causes impaired efflux of cystine from lysosomes to the cytoplasm, where it is normally further processed and then reused. As a result, cystine accumulates in lysosomes, forming crystals that are poorly soluble and hexagonal, rectangular, or needle-shaped. Cystine crystals are thought to induce cellular apoptosis, which leads to dysfunction in multiple organ systems.

The most prominent defect occurs in the kidneys, where proximal tubular dysfunction leads to impaired reabsorption of electrolytes, water, amino acids, glucose, bicarbonate, and other molecules, a phenomenon known as the renal Fanconi syndrome (FS). The cellular mechanism of renal FS in this instance, however, is not well understood. Tubular and interstitial cystine accumulation may impede the normal transport and cotransport of small molecules in tubular cells; however, recent studies indicate that lysosomal cystine accumulation disrupts the interaction of lysosomes and mitochondria needed for normal apoptotic and autophagic processes. The result is adenosine triphosphate (ATP) deficiency, which leads to intracellular energy depletion, oxidative stress, and inexorable deterioration of renal cell function.

PRESENTATION AND DIGANOSIS

The typical child with cystinosis appears normal at birth and then presents between 6 and 12 months of age as a small, listless infant. Early diagnosis is critical so that life-saving treatment may be rapidly instituted.

The most striking features are usually referable to the presence of renal FS, which causes polyuria, proximal renal tubular acidosis (see Plate 3-25), and wasting of electrolytes, glucose, amino acids, carnitine, and tubular proteins. The profound homeostatic abnormalities that result can cause failure to thrive, cardiac dysfunction, muscle hypotonia, and hypophosphatemic rickets. In some patients who present later in infancy, one of these sequelae may be the presenting complaint.

Any patient found to have renal FS should undergo slit lamp examination because corneal cystine crystal accumulation occurs in all patients by 16 months of age. The presence of both renal FS and corneal crystals is diagnostic of NC. The clinical diagnosis can be confirmed by measuring cystine concentrations in polymorphonuclear leukocytes using mass spectroscopy or the cystine binding protein assay. Targeted testing for a panel of *CTNS* mutations, including the most common 57-kb deletion, is also available.

If corneal crystals are not seen, other inherited or acquired causes of renal FS should be investigated, such as heavy metal poisoning, adverse medication effect, multiple myeloma, hereditary fructose intolerance, galactosemia, Dent disease, and Lowe disease.

Prenatal diagnosis can be performed if there is a family history of cystinosis. Elevated cystine concentrations may be noted in the placenta, cultured skin fibroblasts, amniocytes, and chorionic villus cells.

Because of dramatic improvements in the average lifespan of an affected patient, several additional

CYSTINOSIS *(Continued)*

sequelae of this disorder are becoming better appreciated. Some of the many manifestations, grouped by organ system, include:

Renal Disease. In addition to renal FS, patients develop medullary nephrocalcinosis (secondary to phosphaturia and calciuria) and renal insufficiency that eventually leads to end-stage renal failure. In untreated patients, renal insufficiency becomes apparent by 5 years of age.

Ocular Disease. As corneal crystal accumulation becomes severe, it may cause photophobia and blepharospasm. Visual loss may occur if the retina is involved.

Endocrine Disease. Patients often develop hypothyroidism late in the first decade of life. Males develop primary testicular hypogonadism that leads to delayed puberty and infertility, while females have spared ovarian and reproductive functions. A subset of patients may develop pancreatic insufficiency, with resulting failure of endocrine function (leading to type 1 diabetes mellitus) and/or exocrine function (leading to intestinal malabsorption).

Muscle Disease. Patients develop myopathies later in life that begin as distal muscle weakness and atrophy, then progress to involve the oropharyngeal muscles, causing dysphagia, malnutrition, and risk of aspiration. Thoracic muscle weakness can cause restrictive pulmonary disease.

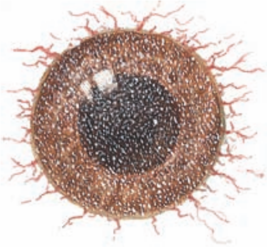
Cardiovascular Disease. Vascular calcification may occur, including in the coronary arteries.

Gastrointestinal Disease. Patients may develop hepatic nodular regenerative hyperplasia, leading to hepatomegaly and portal hypertension. Inflammatory bowel disease and bowel perforation have been noted in some patients.

Central Nervous System Disease. Cerebral atrophy, calcifications of the basal ganglia, and benign intracranial hypertension (causing headaches and papilledema) may be seen. Cognitive abilities are in the low-normal range in most patients, but specific neurologic and neurobehavioral issues are characteristic, including visual memory defects.

Hematologic Disease. Although cystine accumulates in bone marrow, hematopoietic function generally remains stable. Anemia may nonetheless occur, however, as chronic kidney disease becomes more advanced.

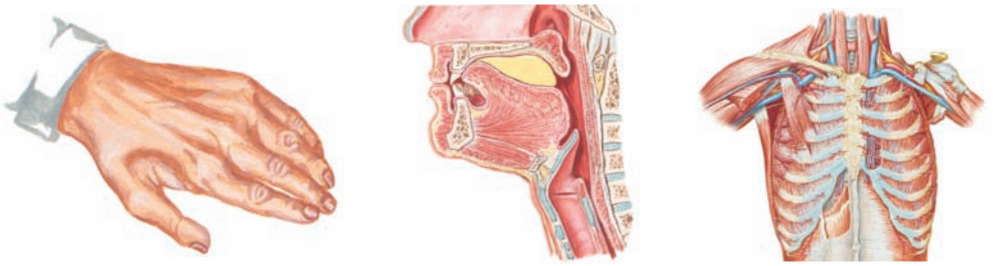
EXTRARENAL MANIFESTATIONS OF CYSTINOSIS



Corneal crystal deposition, which can lead to photophobia, blepharospasm, and blinding retinopathy

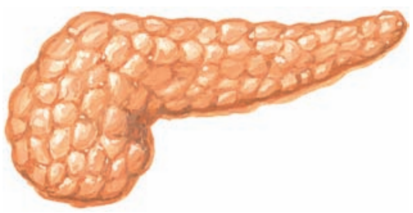
Hypothyroidism

Primary hypogonadism in males, with delayed puberty and infertility

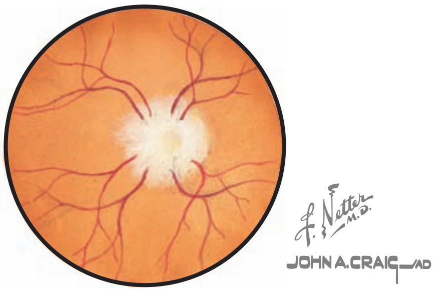


Myopathy, which begins as distal muscle weakness and atrophy. Later, oropharyngeal involvement can lead to dysphagia, while extrinsic chest muscle involvement can cause restrictive pulmonary disease.

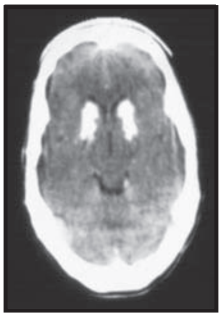
Hepatic nodular regenerative hyperplasia, with hepatomegaly and portal hypertension



Pancreatic insufficiency, exocrine and/or endocrine



Benign intracranial hypertension, causing headaches and papilledema



Calcifications of the basal ganglia

TREATMENT

The treatment of cystinosis can be divided into symptomatic and pathophysiologic management.

Symptomatic management addresses the numerous complications of cystine accumulation in different organ systems. The major early complication is renal FS, as described previously, which must be treated with replacement of wasted fluids, electrolytes (including potassium, phosphate, and bicarbonate), vitamin D, and carnitine.

To address the many additional complications listed previously, follow-up care should include measurement of serum creatinine concentration, thyroid panels, insulin levels, lipid panels, testosterone, and sex hormone levels; glucose tolerance tests; electromyography; barium swallow studies; computed tomography of the brain and chest (for detecting calcification of cerebral and other major vessels); renal ultrasonography (to assess for nephrocalcinosis); and pulmonary function tests.

As renal disease progresses, renal replacement therapy is commonly required. Transplantation of both living donor and cadaveric kidneys has led to excellent outcomes, with no recurrence of renal FS in the donor kidney.

Pathophysiologic management, meanwhile, involves the use of cystine-depleting agents to actually slow disease progression. Cysteamine, an aminothiol, reacts with cystine to form cystine-cysteamine mixed disulfide and cysteine, which exit the lysosome via lysine and cysteine transporters, respectively. As a result, cysteamine depletes intracellular cystine levels by 90%. Oral cysteamine is indicated for all patients, independent of age and transplantation status. Meanwhile, topical cysteamine eye drops can also dissolve corneal crystals and ameliorate the photophobia of cystinosis within a few weeks. Regular measurement of the leukocyte cystine level documents the efficacy of treatment.

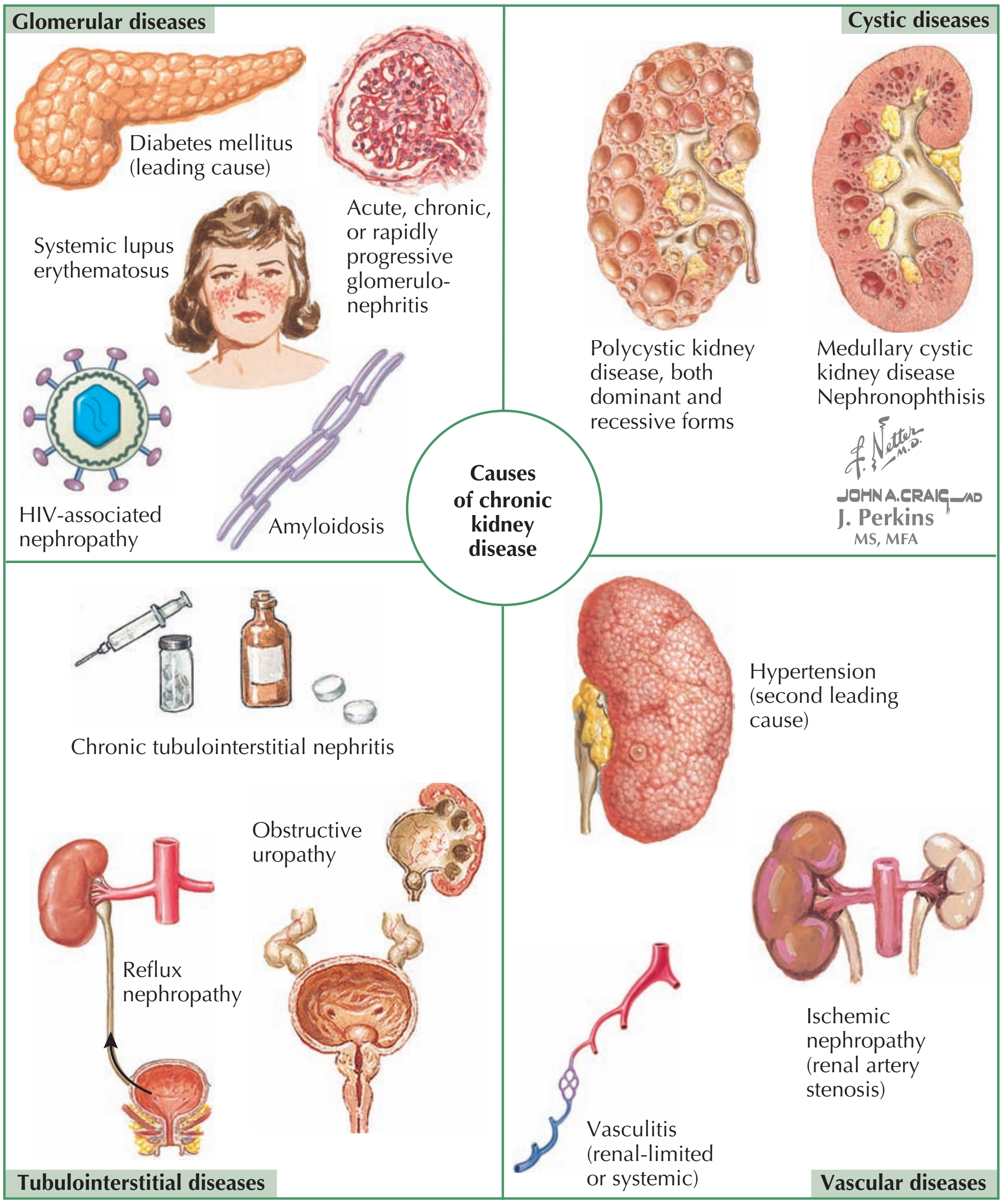
PROGNOSIS

The use of cystine-depleting therapy has revolutionized the prognosis of NC. With prompt and compliant cysteamine treatment, many children do not develop renal failure until their second or third decade of life. The severity of the various complications depends largely on genetic heterogeneity and compliance with medical therapy. Most complications are preventable and possibly even reversible with optimal treatment. Newborn screening for early diagnosis will further advance the treatment of cystinosis.

STAGING SYSTEM AND MAJOR CAUSES OF CHRONIC KIDNEY DISEASE

Staging system (National Kidney Foundation)

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal GFR	>90
2	Mild reduction in GFR	60–89
3	Moderate reduction in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure	<15 (or dialysis)


Glomerular diseases
Diabetes mellitus (leading cause)
Acute, chronic, or rapidly progressive glomerulonephritis
Systemic lupus erythematosus
HIV-associated nephropathy
Amyloidosis
Cystic diseases
Polycystic kidney disease, both dominant and recessive forms
Medullary cystic kidney disease Nephronophthisis
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JOHN A.CRAIG AD
J. Perkins MS, MFA
Causes of chronic kidney disease
Chronic tubulointerstitial nephritis
Obstructive uropathy
Reflux nephropathy
Tubulointerstitial diseases
Hypertension (second leading cause)
Ischemic nephropathy (renal artery stenosis)
Vasculitis (renal-limited or systemic)
Vascular diseases

OVERVIEW OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) affects over 26 million adults in the United States and is defined as 3 or more months of either (1) histopathologic or functional evidence of kidney damage, or (2) a glomerular filtration rate less than 60 mL/min/1.73 m^2. CKD is classified into five stages based on the degree of functional impairment, as inferred from estimations of glomerular filtration rate.

CKD can be caused by numerous underlying processes. In general, causes can be grouped into glomerular diseases (such as diabetic nephropathy or lupus nephritis), vascular diseases (such as hypertension), tubulointerstitial diseases (such as obstructive uropathy), and cystic diseases. The most common causes are diabetes mellitus and hypertension, which together account for over two thirds of cases.

PATHOPHYSIOLOGY

Irrespective of the primary renal disease, the kidney initiates a compensatory response to nephron loss that is initially adaptive but ultimately causes further loss of function. Thus the progression of CKD depends in part on mechanisms that are independent of the inciting disease process.

In particular, loss of a subset of nephrons results in compensatory hyperfiltration and hypertrophy of the remaining functional nephrons, an effect likely mediated by angiotensin II, aldosterone, endothelin, and other hormones. The resulting intraglomerular hypertension, however, eventually becomes maladaptive, inflicting damage to the remaining nephrons and thereby causing a further decline in overall filtration. In the glomerulus, podocyte (visceral epithelial cell) foot process effacement and denudation may lead to a breakdown of the protein filtration barrier and glomerulosclerosis. The ensuing proteinuria is thought to further promote kidney failure by exerting toxic effects on the tubules. In addition, mesangial cells respond to the increased pressure with proliferation and production of increased extracellular matrix; these changes stimulate inflammation and cellular infiltration of the mesangium and tubulointerstitium, leading to tubulointerstitial fibrosis.

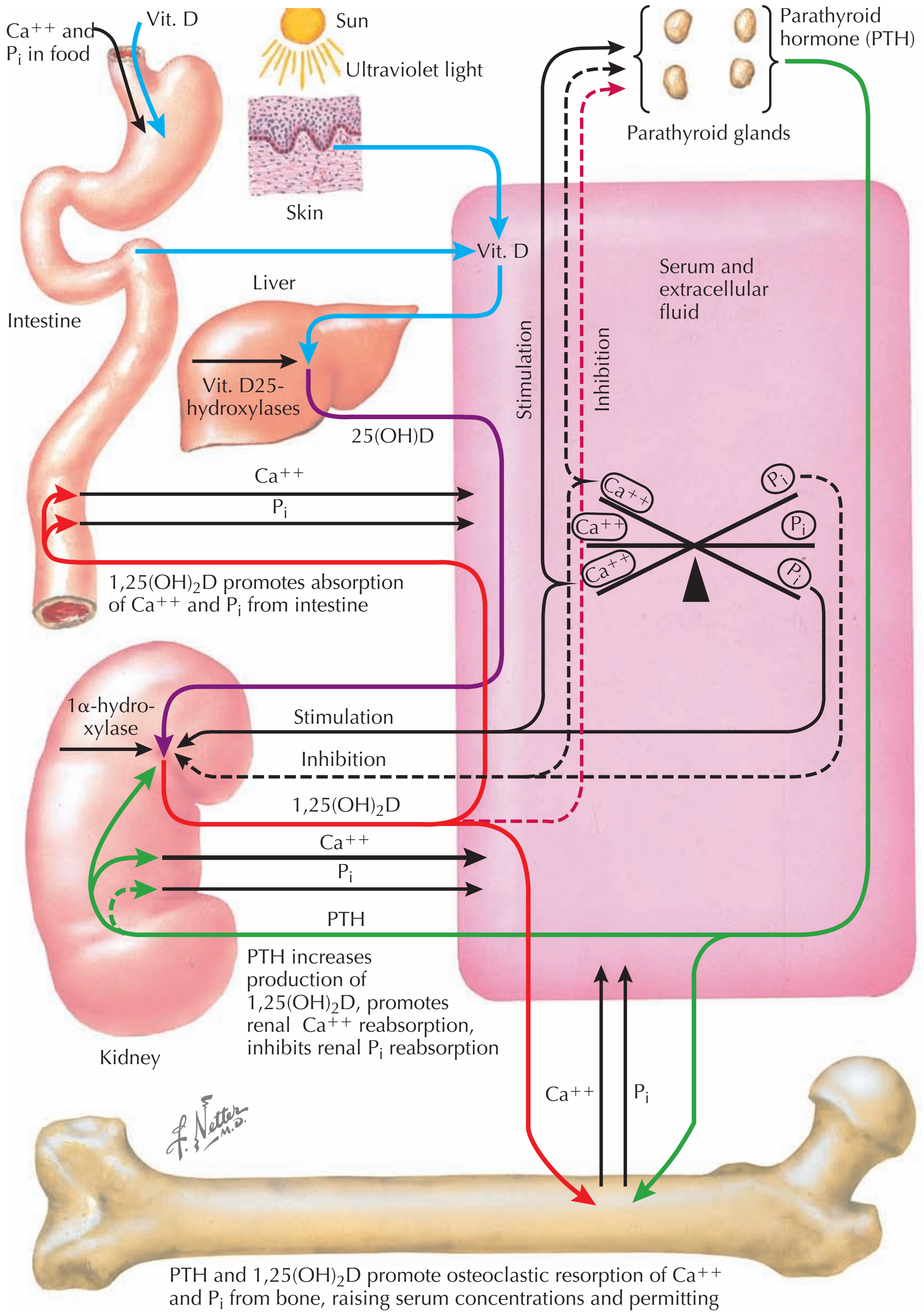
A significant number of nephrons must be lost before these maladaptive changes are seen, and the exact quantity varies between species and individuals. In rats, for example, one and 5/6 nephrectomy must be performed to create a model of progressive renal insufficiency. In humans, it is well-known that donation of one entire kidney does not generally result in loss of overall renal function. In those individuals who do lose enough functional renal mass to experience the maladaptive effects of hyperfiltration, the rate of further functional decline is also variable, depending on the primary inciting factor, patient age, and possibly genetic factors.

ASSESSMENT OF RENAL FUNCTION

The serum creatinine concentration should be used to estimate the creatinine clearance or GFR (eGFR), which can be accomplished using the Cockcroft-Gault formula or the modification of diet in renal disease (MDRD) study equation, respectively.

Current guidelines recommend that serum creatinine concentration be measured at least once per year in

NORMAL CALCIUM AND PHOSPHATE METABOLISM


Ca^{++} and P_i in food
Vit. D
Sun
Ultraviolet light
Parathyroid hormone (PTH)
Parathyroid glands
Skin
Vit. D
Serum and extracellular fluid
Liver
Intestine
Vit. D25-hydroxylases
25(OH)D
Stimulation
Inhibition
Ca^{++}
P_i
$1,25(OH)_2D$ promotes absorption of Ca^{++} and P_i from intestine
1α-hydroxylase
Stimulation
Inhibition
$1,25(OH)_2D$
Ca^{++}
P_i
PTH
PTH increases production of $1,25(OH)_2D$, promotes renal Ca^{++} reabsorption, inhibits renal P_i reabsorption
Kidney
Ca^{++}
P_i
F. Netter M.D.
PTH and $1,25(OH)_2D$ promote osteoclastic resorption of Ca^{++} and P_i from bone, raising serum concentrations and permitting normal mineralization

OVERVIEW OF CHRONIC KIDNEY DISEASE *(Continued)*

patients with CKD. The frequency should be increased in those with an eGFR <60 mL/min/1.73 m^2, loss of >4 mL/min/1.73 m^2 per year of eGFR, or with risk factors for progression (high level of proteinuria, hypertension, diabetes mellitus).

Patients should be referred to a nephrologist when the eGFR falls below 30 mL/min/1.73 m^2, or sooner if the primary care physician is unable to carry out a treatment plan for CKD.

COMPLICATIONS AND MANAGEMENT

Patients with CKD are typically asymptomatic until the disease process becomes advanced. Thus it is important to screen for CKD and its complications in high-risk patients, such as those with diabetes mellitus and/or hypertension, so that treatment can be initiated at an early stage.

Hypertension. Hypertension is both a cause and consequence of progressive chronic kidney disease. It is a cause because elevated arterial pressures are transmitted to the glomeruli of the remaining nephrons, exacerbating hyperfiltration and accelerating further nephron loss. It is also a consequence because, as nephron loss progresses, there is ongoing secretion of angiotensin II and impaired excretion of excess sodium and water. Thus more than 75% of patients with CKD suffer from hypertension.

Blood pressure must be routinely measured in all patients, and hypertension must be treated to slow nephron loss. Blood pressure should be kept at 130/80 mm Hg or less, and the mainstays of treatment are medications that block the renin-angiotensin-aldosterone system, including ACE inhibitors and ARBs. These agents preferentially dilate efferent arterioles, lowering intraglomerular pressure. Because of this partial reversal of glomerular hyperfiltration, there is an expected and acceptable 30% increase in serum creatinine; however, providers should carefully monitor patients for both acute declines in eGFR and hyperkalemia.

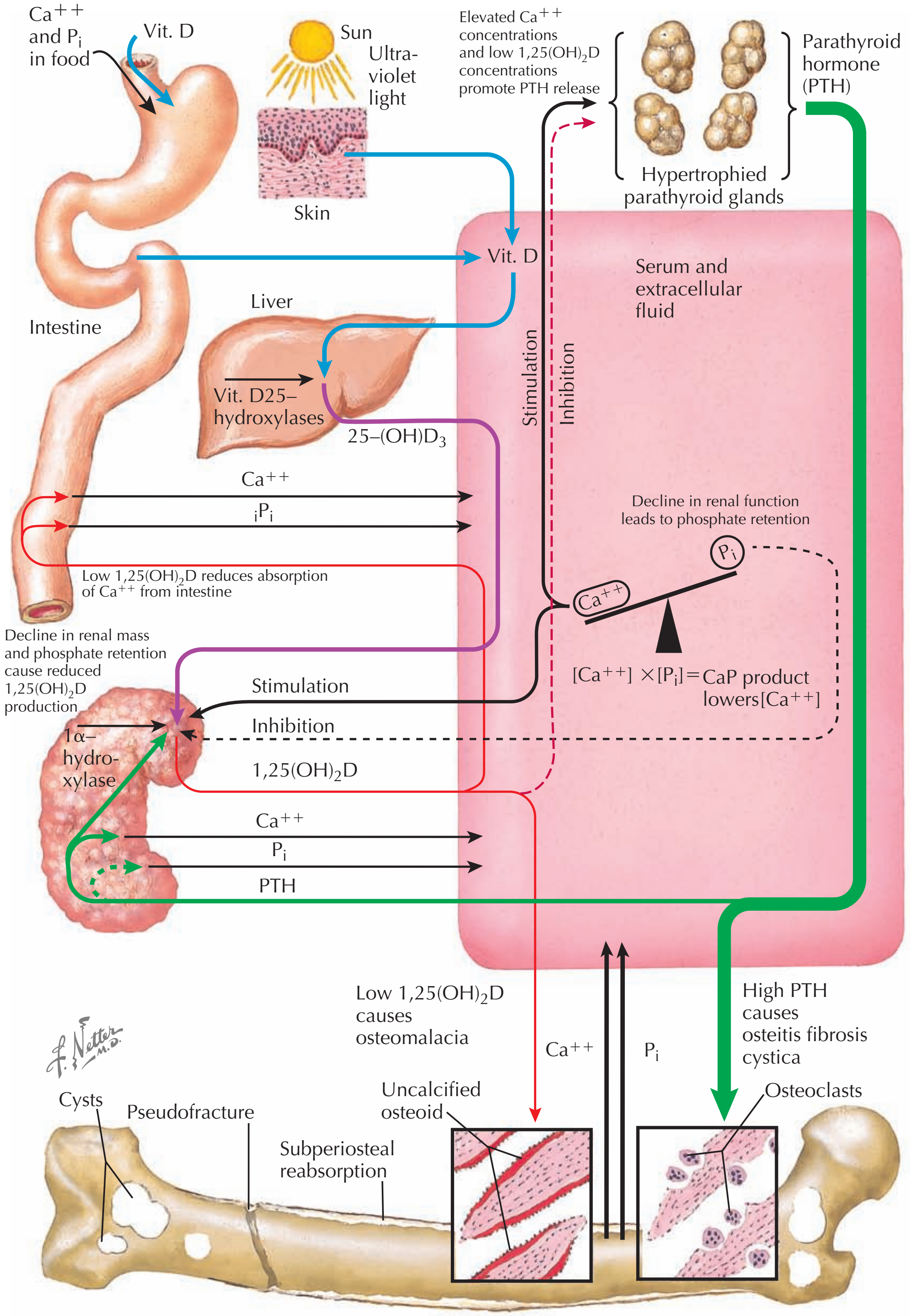
Diuretics are often needed as well, especially as more advanced disease leads to greater retention of sodium and water. In general, at an eGFR <30 mL/min/1.73 m^2, loop diuretics are more effective than thiazide diuretics. Patients should also be strongly encouraged to maintain a low-salt diet.

Proteinuria. Proteinuria is a marker of glomerular injury, but it is also understood to contribute to CKD progression. In particular, proteins that are filtered in the glomerulus are reabsorbed in proximal tubule cells, where they trigger inflammation, apoptosis, and fibrosis. In addition, abnormal filtration of growth factors and cytokines also promotes tubular injury. Thus a reduction in proteinuria has been associated with a slower progression of chronic kidney disease, particularly among patients with diabetic disease.

Proteinuria must be regularly assessed in all patients. In nondiabetics, screening with urine dipstick is acceptable, but if positive, a spot urine protein : creatinine ratio should be performed for quantification. A 24-hour urine collection for protein can be performed; however, a spot sample is typically adequate and is easier for the patient. In diabetics, regular screening for microalbuminuria should be performed early in the disease course.

ACE inhibitors and ARBs have been shown to reduce proteinuria, likely because of the reduction in intraglomerular pressure. Studies in diabetic patients have shown that these drugs reduce proteinuria and slow the

CALCIUM AND PHOSPHATE METABOLISM IN CHRONIC KIDNEY DISEASE


Ca++ and Pi in food
Vit. D
Sun
Ultra-violet light
Skin
Elevated Ca++ concentrations and low 1,25(OH)2D concentrations promote PTH release
Parathyroid hormone (PTH)
Hypertrophied parathyroid glands
Vit. D
Serum and extracellular fluid
Stimulation
Inhibition
Intestine
Liver
Vit. D25–hydroxylases
25–(OH)D3
Ca++
iPi
Low 1,25(OH)2D reduces absorption of Ca++ from intestine
Decline in renal function leads to phosphate retention
Pi
Ca++
[Ca++] × [Pi] = CaP product lowers [Ca++]
Decline in renal mass and phosphate retention cause reduced 1,25(OH)2D production
Stimulation
Inhibition
1α–hydroxylase
1,25(OH)2D
Ca++
Pi
PTH
Low 1,25(OH)2D causes osteomalacia
Ca++
Pi
High PTH causes osteitis fibrosis cystica
Cysts
Pseudofracture
Subperiosteal reabsorption
Uncalcified osteoid
Osteoclasts
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OVERVIEW OF CHRONIC KIDNEY DISEASE *(Continued)*

decline of eGFR independent of their effect on systemic blood pressure.

Bone Disease. Renal disease also leads to numerous morphologic changes in bone, a group of phenomena collectively known as renal osteodystrophy. This disorder encompasses a spectrum of disease with both high bone turnover (osteitis fibrosa cystica) and low bone turnover (adynamic bone disease and osteomalacia).

Osteitis fibrosa cystica, a high turnover disease, reflects secondary hyperparathyroidism and is associated with bone pain and an increased risk of fracture. High PTH levels are often seen once the eGFR declines to less than 60 mL/min/1.73 m^2 (stage 3 CKD), and they are invariably seen when eGFR is less than 30 mL/min/1.73 m^2 (stage 4 CKD). High PTH levels initially occur because of decreased renal production of 1,25(OH)$_2$D, the activated form of vitamin D, which results from both a reduction in renal mass and impaired renal excretion of phosphate. The decline in 1,25(OH)$_2$D stimulates PTH secretion and, moreover, causes a reduction in intestinal reabsorption of calcium, which further stimulates PTH release. Initially, the high levels of PTH maintain serum phosphate and calcium concentrations within normal range, at the expense of causing bone disease. As renal dysfunction progresses, however, hyperphosphatemia ensues. In addition, hypocalcemia eventually occurs, both because of the decline in 1,25(OH)$_2$D levels and because of formation of soluble calcium-phosphate complexes. Skeletal resistance to PTH, which remains chronically elevated, also appears to play a role.

In patients with stage 3-5 CKD, serum concentrations of PTH, phosphate, and calcium should be checked regularly. According to current guidelines, the goal PTH levels for stage 3 CKD are 35 to 70 pmol/L, for stage 4 CKD are 70 to 110 pmol/L, and for stage 5 CKD are 150 to 300 pmol/L. Goal serum phosphate levels for stages 3 and 4 CKD are 2.7 to 4.6 mg/dL, and for stage 5 CKD are 3.5 to 5.5 mg/dL. To achieve these levels, hyperphosphatemia is typically addressed first using a low phosphorous diet and phosphate binders. Either calcium or noncalcium containing binders may be used, with the choice sometimes depending on the patient's serum calcium concentration. Vitamin D (25-OH) levels should also be checked, and if levels are below 30 μg/mL, supplemental ergocalciferol may be offered.

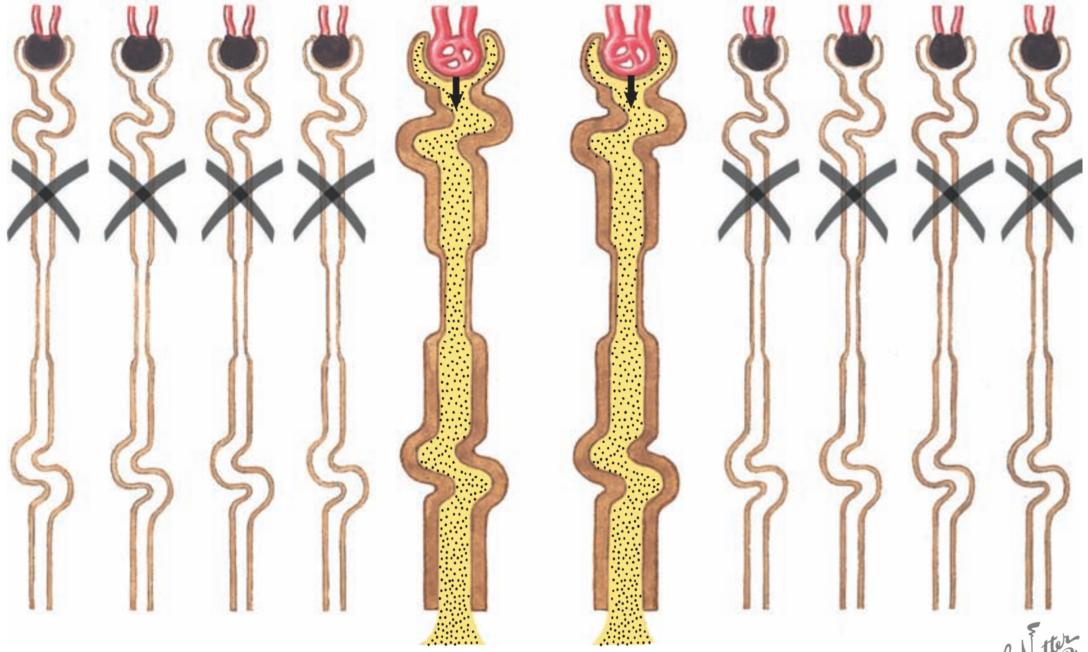
If PTH levels remain elevated despite these measures, active vitamin D analogues (such as calcitriol) may be used in lieu of ergocalciferol; however, these agents may cause marked elevation of serum phosphate and calcium levels, which must continue to be carefully monitored. In patients with more advanced disease, calcimimetics (i.e., cinacalcet) may be used, although they are only approved for those receiving dialysis. Calcimimetics bind to the calcium sensing receptor on the parathyroid glands, suppressing PTH release, but they are associated with an increased risk of hypocalcemia.

If PTH levels are oversuppressed, patients can develop adynamic bone disease, which is also associated with increased risk of fracture. This disorder is becoming increasingly common as vitamin D analogues are more widely used to suppress PTH. If the PTH level falls below 100 pmol/L, the risk of adynamic bone disease is high, and dosages of vitamin D analogues and calcium-based phosphate binders should be reduced.

Finally, osteomalacia, another form of low bone turnover disease, can be seen in some patients due to vitamin

MECHANISM OF PROGRESSION AND COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Loss of a significant number of nephrons leads to hyperfiltration and hypertrophy of the remaining nephrons, which temporarily maintains filtration function. Over time, however, intraglomerular hypertension damages the remaining nephrons, which are gradually lost as well. Thus, patients with chronic kidney disease often have a progressive loss of renal function, even if the process initially responsible for their kidney injury has resolved.



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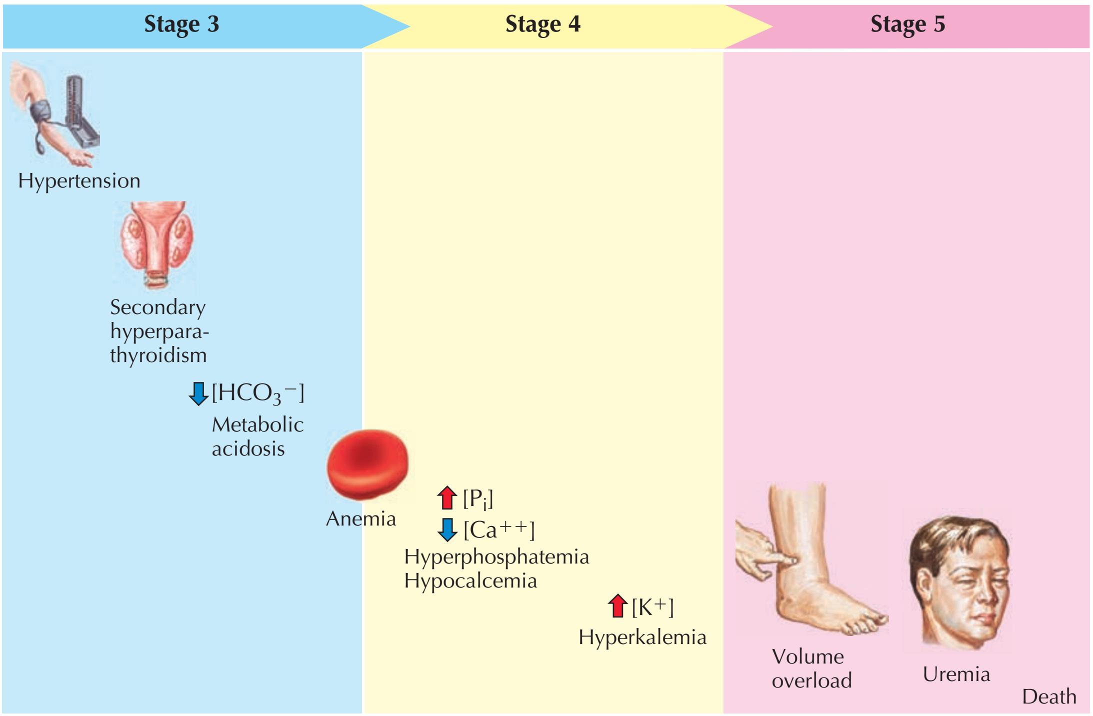
Complications and stage of onset

The exact timing and sequence of these complications vary among patients.



OVERVIEW OF CHRONIC KIDNEY DISEASE *(Continued)*

D deficiency or aluminum toxicity. With the near elimination of aluminum-based binders in clinical practice, however, aluminum toxicity is now uncommon.

The specific type of bone disease can be definitively diagnosed with bone biopsy, which is not routinely performed in clinical practice. Instead, the presence of bone disease is typically inferred from abnormal PTH levels.

Acidosis. Once GFR declines to 40 to 50 mL/min/1.73 m^2, patients are not able to excrete their daily acid load. The remaining functioning nephrons have maximized their ammonium excretion, and excretion of titratable acids may also be reduced because of the dietary restriction of phosphate and use of phosphate binders. The result is metabolic acidosis with a positive anion gap, which is usually discovered as a low serum bicarbonate level on a routine assessment of serum chemistries. Current guidelines recommend that serum bicarbonate be checked annually in patients with stage 3 CKD and every 3 months in patients with stage 4 or 5 CKD. It is recommended that serum bicarbonate concentrations be maintained at 22 mEq/L or greater. Oral bicarbonate replacement can be used to achieve this goal.

Anemia. CKD leads to normocytic anemia due to inadequate renal production of erythropoietin. Anemia is sometimes seen in stage 3 CKD and is almost always seen in stage 4 CKD. Current guidelines recommend that hemoglobin levels be measured annually in any patient with CKD.

In males with hemoglobin less than 13 g/dL and females with hemoglobin less than 12 g/dL, further workup should be performed, including a complete blood count, reticulocyte count, and an assessment of iron stores. Relative iron deficiency is common and contributes to the decreased production of red cells. One reason for iron deficiency is that the inflammatory cytokines released in CKD promote secretion of hepcidin, which blocks iron absorption from the GI tract and iron release from macrophages.

In general, erythropoiesis-stimulating agents are used to maintain a hemoglobin level of 11 to 12 g/dL. The target should not exceed 13 g/dL. In patients receiving this treatment, iron stores should be assessed and replenished as needed to avoid apparent erythropoietin resistance. Oral iron supplements, such as iron sulfate or iron gluconate, are commonly given. If patients are resistant to these supplements because of impaired intestinal absorption, intravenous iron preparations may be used instead.

Cardiovascular Disease. Cardiovascular disease is the leading cause of death among patients with chronic kidney disease, and it affects 40% of dialysis patients compared with 10% of the general population. Patients with CKD are more likely to have classic risk factors for cardiovascular disease, such as hypertension, diabetes mellitus, and hyperlipidemia. CKD itself, however, also appears to be an independent risk factor for CVD, and recent studies have shown a strong correlation between declines in eGFR and increased cardiovascular events.

Numerous factors are responsible for this association. Vascular calcification appears to result from the use of calcium-based phosphate binders and vitamin D analogues. It may affect the intimal layer, leading to atherosclerotic plaques, and/or the medial layer, leading to vessel stiffening. The inflammation and secondary hypertension associated with CKD also accelerate vascular disease.

In addition to increasing the risk for cardiovascular disease, CKD also increases the risk of left ventricular hypertrophy by causing hypertension, anemia, and hypervolemia. The prevalence of left ventricular

OVERVIEW OF CHRONIC KIDNEY DISEASE *(Continued)*

hypertrophy is much higher among dialysis patients than the general population.

Modification of cardiovascular risk factors—such as smoking, hyperlipidemia, and hypertension—should remain a primary focus of therapy. Even after kidney disease becomes more advanced, many patients die from cardiovascular disease before ever reaching end stage renal disease.

Hyperkalemia. Renal excretion of potassium does not become significantly impaired until stage 4 CKD; however, a potassium-rich diet or use of ACE inhibitors/ARBs can lead to hyperkalemia at earlier stages.

A low potassium diet (<50 mEq/day) may be instituted as a preventive measure. In addition, treating metabolic acidosis will lower serum potassium levels, and loop diuretics may be used to promote urinary excretion of potassium. Dialysis may be required if hyperkalemia becomes refractory to medical management.

Volume Overload. Overt symptoms of volume overload, such as peripheral and pulmonary edema, do not typically occur until stage 5 CKD but can be precipitated in earlier stages by increased salt intake or coexisting congestive heart failure. These symptoms can generally be treated with sodium restriction and additional diuretics.

Uremia. As renal dysfunction becomes very advanced, the retention of toxic substances in the general circulation can lead to numerous abnormalities that are together known as uremia. In general, the term is used to describe the effects of those retained toxins that have not been identified or are poorly understood. Signs and symptoms of uremia include loss of appetite, weight loss, fatigue, altered mental status, peripheral neuropathies, nausea, vomiting, pruritus, and platelet dysfunction. Although uremia is associated with an elevated blood urea nitrogen (BUN) concentration, BUN itself is not felt to be the cause of uremia.

ADDITIONAL CONSIDERATIONS

It is essential that renally cleared medications be dosed based on eGFR. Furthermore, drugs that may precipitate an acute decline in renal function, such as nonsteroidal antiinflammatory drugs should be avoided. Careful consideration must be given when administering iodinated contrast due to the risk of acute renal failure. In addition, gadolinium-based contrast should be used judiciously in patients with stage 4 or 5 CKD because of the increased risk of nephrogenic systemic fibrosis.

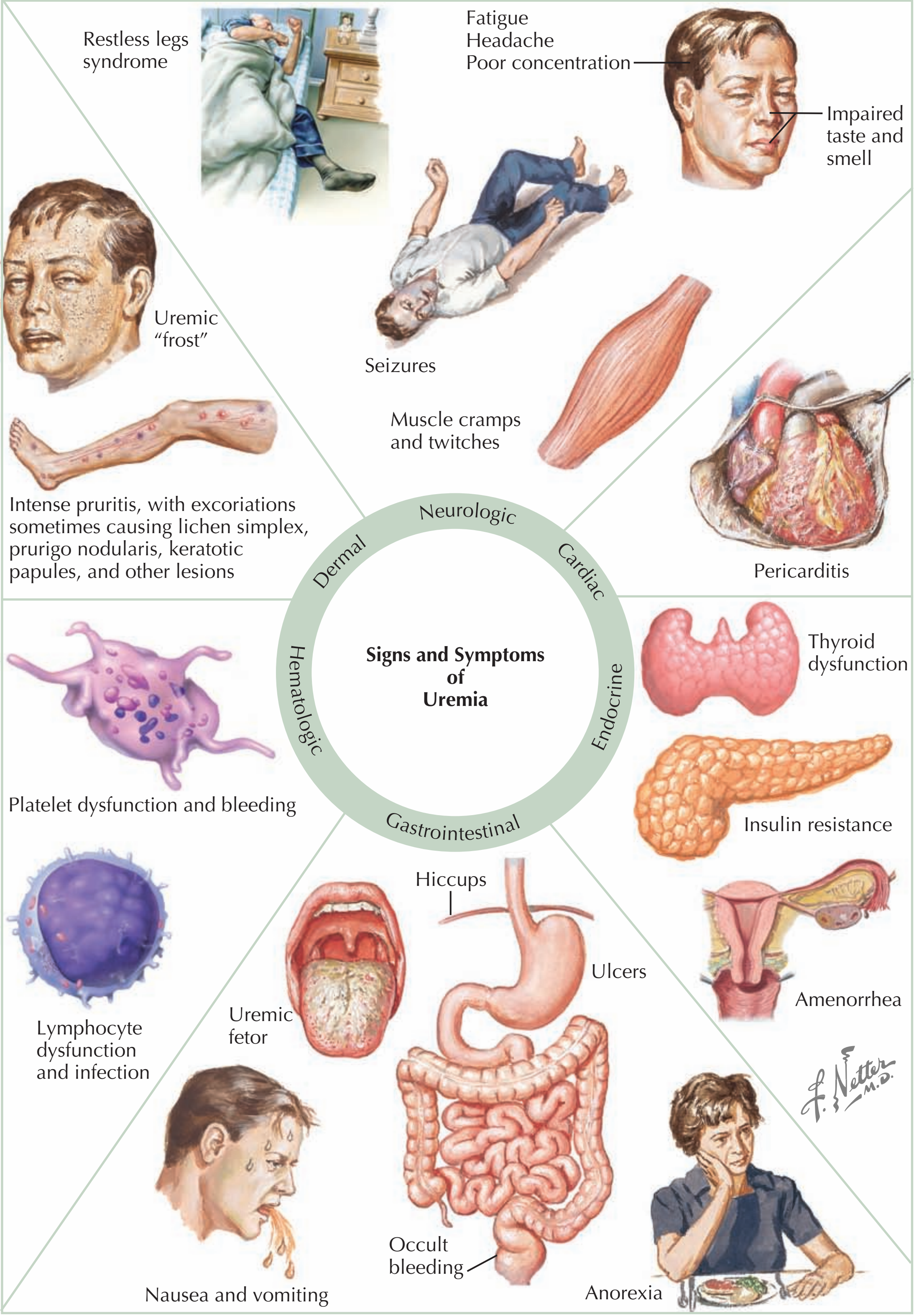
END-STAGE RENAL DISEASE

Ultimately, a small proportion of patients with CKD will progress to end-stage renal disease (ESRD), defined as the need for dialysis therapy or kidney transplantation. The rate of progression, however, is highly variable across patients.

Dialysis is typically initiated when the eGFR falls below 10 mL/min/1.73 m^2; however, there are numerous acute indications as well, which include refractory hyperkalemia, volume overload, and uremia.

In most patients, preemptive kidney transplantation is preferred over ongoing dialysis because the long-term survival is significantly better. Compared with dialysis patients on the transplant list, patients who receive a kidney transplant have an initial increase in mortality; however, at 4 months post-transplant the risk of death is equal between the two groups, and thereafter transplanted patients have a 68% lower risk of mortality compared with patients on dialysis. The survival benefit is particularly robust among patients with diabetes.

UREMIA



Restless legs syndrome
Fatigue
Headache
Poor concentration
Impaired taste and smell
Uremic "frost"
Seizures
Muscle cramps and twitches
Intense pruritis, with excoriations sometimes causing lichen simplex, prurigo nodularis, keratotic papules, and other lesions
Pericarditis
Neurologic
Dermal
Cardiac
Hematologic
Endocrine
Gastrointestinal
Signs and Symptoms of Uremia
Thyroid dysfunction
Platelet dysfunction and bleeding
Insulin resistance
Hiccups
Ulcers
Amenorrhea
Lymphocyte dysfunction and infection
Uremic fetor
Occult bleeding
Nausea and vomiting
Anorexia
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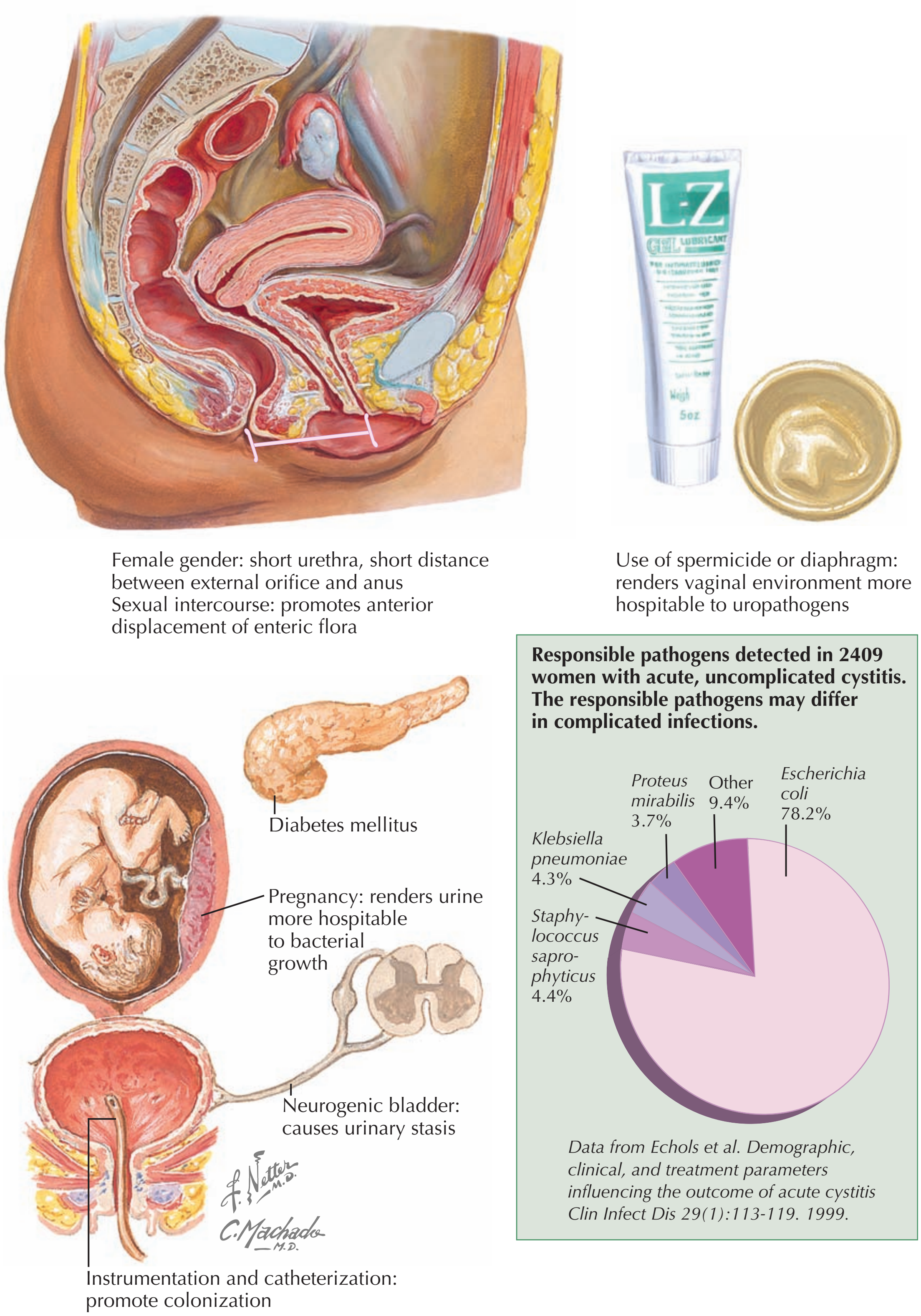
SECTION 5

URINARY TRACT INFECTIONS

RISK FACTORS FOR LOWER URINARY TRACT INFECTION



Female gender: short urethra, short distance between external orifice and anus
Sexual intercourse: promotes anterior displacement of enteric flora

Use of spermicide or diaphragm: renders vaginal environment more hospitable to uropathogens

Diabetes mellitus

Pregnancy: renders urine more hospitable to bacterial growth

Neurogenic bladder: causes urinary stasis

Instrumentation and catheterization: promote colonization

Responsible pathogens detected in 2409 women with acute, uncomplicated cystitis. The responsible pathogens may differ in complicated infections.

Proteus mirabilis 3.7%
Other 9.4%
Escherichia coli 78.2%
Klebsiella pneumoniae 4.3%
Staphylococcus saprophyticus 4.4%

Data from Echols et al. Demographic, clinical, and treatment parameters influencing the outcome of acute cystitis Clin Infect Dis 29(1):113-119. 1999.

CYSTITIS

Urinary tract infections (UTIs) can involve the bladder alone (lower UTI, also known as acute cystitis) or extend to the renal pelvis and parenchyma (upper UTI, also known as acute pyelonephritis). If untreated, such infections can progress in vulnerable hosts to systemic bacterial disease, known as urosepsis.

Although "cystitis" refers, in the strictest sense, to inflammation of the bladder, by far the most common cause is bacterial infection, which occurs when bacteria ascend to the bladder from the urethra. Thus use of the term "cystitis" without additional qualification usually implies bacterial infection of the bladder. In contrast, "nonbacterial cystitis" is often used to specify bladder inflammation associated with viruses, parasites, radiation, chemical irritants, and other agents.

Cystitis is considered "uncomplicated" when it occurs in women with anatomically and neurologically normal urinary tracts. In contrast, cystitis is considered "complicated" when it occurs in the setting of structural or functional abnormalities of the urinary tract; in association with an indwelling urinary catheter; in conjunction with an upper urinary tract infection; or in men, pregnant women, or hospitalized patients.

PATHOPHYSIOLOGY

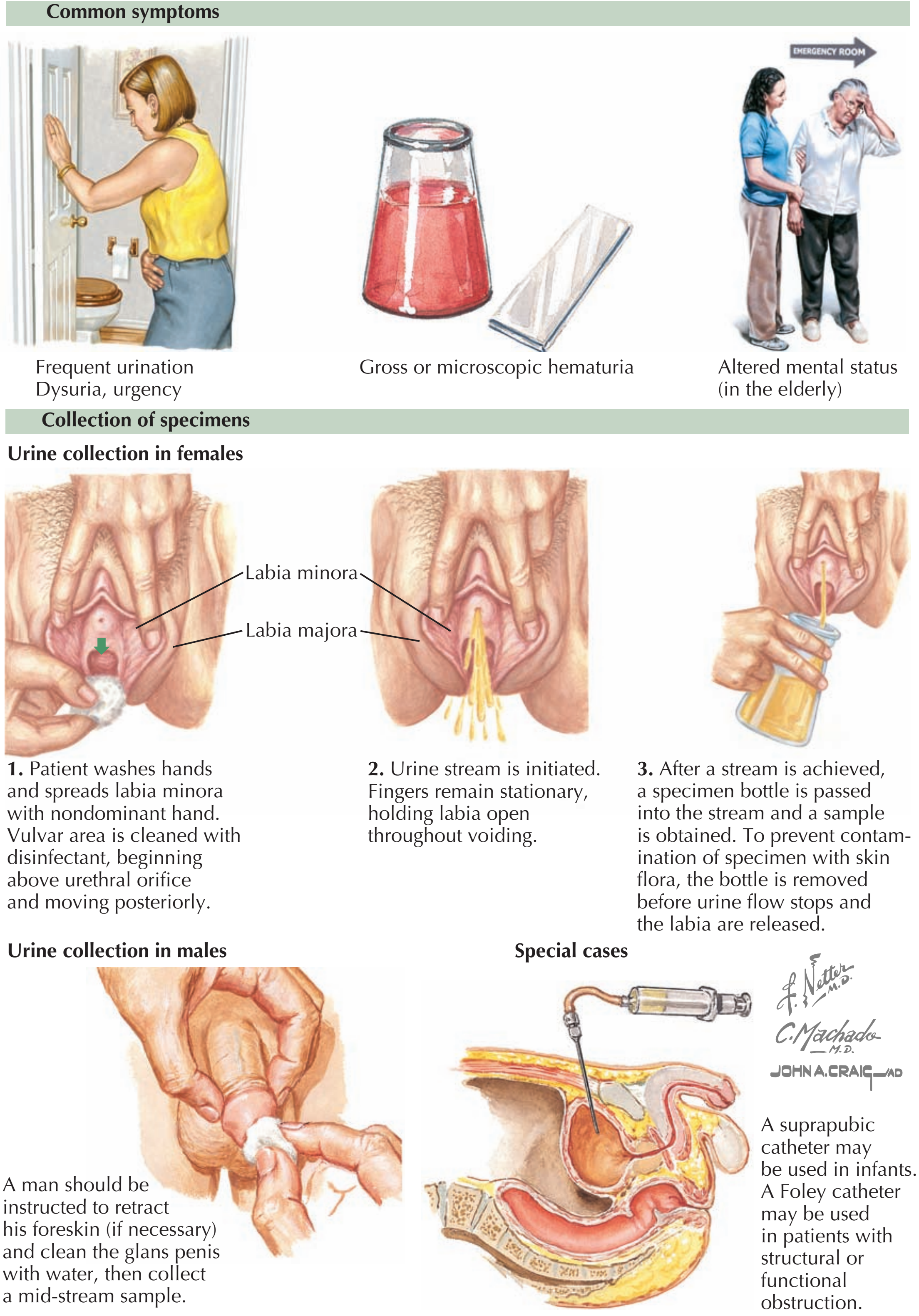
Acute uncomplicated cystitis occurs in women when enteric flora from the perianal region colonize the adjacent vaginal introitus and then ascend the urethra to reach the bladder. *Escherichia coli* (*E. coli*) is the most common pathogen, accounting for nearly 80% of all infections. Other common pathogens include *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, in order of descending frequency. Less commonly, *Citrobacter* and *Enterococcus* may be responsible.

Complicated cystitis, in contrast, often involves additional pathogenetic mechanisms, such as the presence of a urinary catheter or bladder outlet obstruction, and in these cases the responsible pathogens differ. *E. coli*, for example, accounts for only 35% of such infections. Instead, there is a higher prevalence of other gram-negative species, such as *Pseudomonas aeruginosa*, and gram-positive organisms, such as *Enterococcus* and coagulase-negative staphylococci.

In any patient, the likelihood of urinary tract infection depends on the balance between host defenses and pathogen virulence factors. In the host, several mechanisms defend the urinary tract from infection. For example, the low pH and high urea concentration in urine inhibit bacterial proliferation. In addition, the presence of certain molecules on the epithelial surface of the urinary tract—such as human defensins, Tamm-Horsfall proteins, and glycosaminoglycans—confer protection against bacterial adhesion. Lastly, the flow of urine itself plays an important mechanical role in the clearance of bacteria.

These protective mechanisms, however, may be overcome or impaired in certain circumstances. For example, when women engage in sexual intercourse, there is often substantial displacement of both fecal and vaginal flora toward the urethra. This risk further increases with the use of diaphragms or spermicides, which may render the vaginal environment more hospitable to the proliferation of uropathogens. In older women, a decline in estrogen can lead to a loss of the protective lactobacilli that are part of the normal vaginal flora,

COMMON SYMPTOMS AND TESTS FOR URINARY TRACT INFECTION



Common symptoms

Frequent urination
Dysuria, urgency

Gross or microscopic hematuria

Altered mental status
(in the elderly)

Collection of specimens

Urine collection in females

1. Patient washes hands and spreads labia minora with nondominant hand. Vulvar area is cleaned with disinfectant, beginning above urethral orifice and moving posteriorly.

2. Urine stream is initiated. Fingers remain stationary, holding labia open throughout voiding.

3. After a stream is achieved, a specimen bottle is passed into the stream and a sample is obtained. To prevent contamination of specimen with skin flora, the bottle is removed before urine flow stops and the labia are released.

Urine collection in males

A man should be instructed to retract his foreskin (if necessary) and clean the glans penis with water, then collect a mid-stream sample.

Special cases

A suprapubic catheter may be used in infants. A Foley catheter may be used in patients with structural or functional obstruction.

CYSTITIS *(Continued)*

enabling increased colonization with uropathogens. Pregnancy alters the pH and osmolality of urine, making it more favorable to bacterial growth.

Several pathologic conditions can also interfere with normal host defenses and increase the likelihood of infection. Diabetes mellitus, for example, has several pathologic effects that predispose affected individuals to infection. Urinary stasis, which can result from anatomic or functional obstruction, makes it more difficult to clear bacteria from the bladder. Indwelling urinary catheters also increase the infection risk by facilitating migration of uropathogens into the bladder. Bacteria adhere to the catheter surface and contribute to the creation of a biofilm, which contains bacteria, bacterial glycocalyces, host proteins, and urinary salts such as apatite and struvite. The bacteria can then travel along the catheter beneath this biofilm until they reach the bladder. Indeed, long-term use of urinary catheters will always result in colonization and infection. In contrast, urinary catheters that are used for fewer than 7 days are less likely to cause clinically significant infections as long as the catheter connections are left undisturbed and a closed drainage system is scrupulously maintained.

Uropathogenic organisms also have several factors that determine their invasiveness, persistence, and site of infection. Genetic differences both within and across species can modulate adhesion to host cells and resistance to the defenses described above. For example, some serogroups of *E. coli* have surface fimbriae that offer improved adhesion and facilitate extension to the upper urinary tract. Similarly, bacteria that express K capsular antigens, such as *Klebsiella* species, are resistant to neutrophil phagocytosis. Finally, motility mechanisms, such as flagellation, permit certain bacteria to navigate the urinary tract against the flow of micturition.

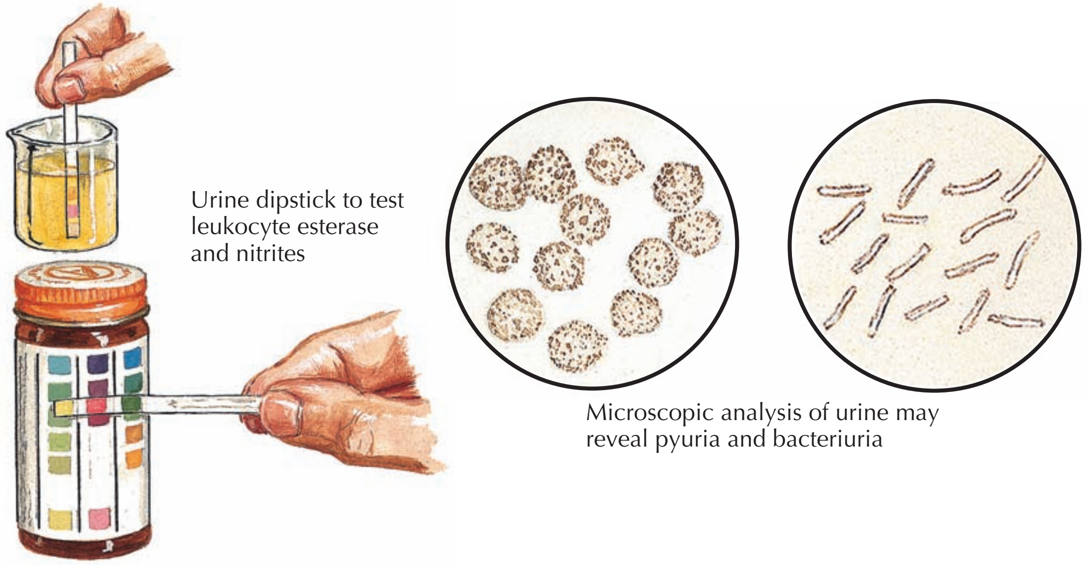
PRESENTATION AND DIAGNOSIS

The major symptoms of cystitis include painful and frequent urination, urgency, hesitancy, and pelvic pressure. These symptoms reflect irritation of urethral and vesicular mucosa. Foul smelling, discolored, or blood-tinged urine may also be noted. The presence of fever or abdominal pain should prompt suspicion for upper tract disease (see Plate 5-5).

In certain populations, such as the elderly, symptoms may be less specific and include depressed mental status and failure to thrive, or there may be no symptoms at all. Children less than 2-years-old may have nonlocalizing symptoms. These differences likely reflect an inability to mount an efficient immune response.

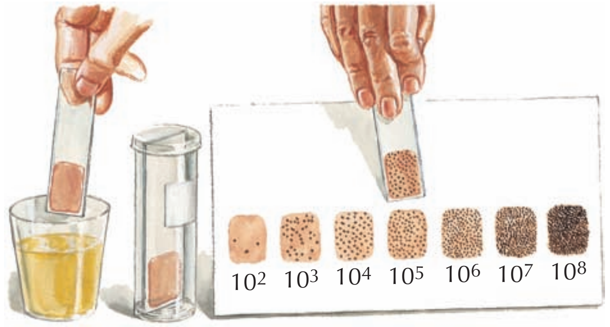
Because urethritis can sometimes mimic the symptoms of cystitis, patients should be evaluated for possible gonorrhea or *Chlamydia* urethritis, as well as for bacterial vaginitis or genital herpes. In addition, the differential must include the numerous causes of nonbacterial cystitis. For example, trauma may cause bladder inflammation and is often seen in women after forceful sexual intercourse. Interstitial cystitis (also known as bladder pain syndrome) may also be associated with cystitis-like symptoms. Hemorrhagic cystitis is most commonly seen in patients undergoing cyclophosphamide treatment but can also result from

EVALUATION OF LOWER URINARY TRACT INFECTION


Urine dipstick to test leukocyte esterase and nitrites
Microscopic analysis of urine may reveal pyuria and bacteriuria

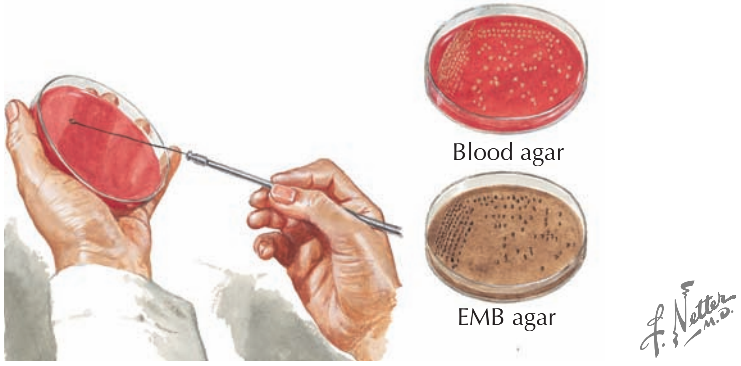
Urine culture quantifies degree of infection and characterizes pathogen

Dip slides



The slide is dipped in urine, allowed to dry, and then incubated in a plastic bottle. One side of the slide contains a general soy agar, which grows both Gram positive and negative bacteria, while the other side contains eosin methylene blue (EMB) agar or MacConkey's agar, which grows Gram negative bacteria. After several days, the growth is compared with a visual reference.

Direct plating



Agar plates are inoculated with urine. A calibrated loop is used to deliver a precise quantity of urine to each plate. Blood agar grows Gram positive and negative bacteria, while EMB agar grows Gram negative bacteria. By counting the number of colonies that grow, the number of colonies that would form per milliliter of urine can be estimated. For example, if 100 colonies appear after 0.001 mL of urine is transferred to the plate, the reported colony count is 100,000 CFU/mL. The colonies can subsequently be sub-cultured for identification and determination of antibiotic susceptibilities.

CYSTITIS *(Continued)*

adenovirus infection, especially in children. Finally, radiation therapy can cause cystitis secondary to scarring.

After a careful history is taken to assess for the above diagnoses, a midstream urine sample should be collected in a sterile fashion and sent for urinalysis with microscopic evaluation. On urine dipstick, a positive leukocyte esterase indicates the presence of white blood cells, whereas positive urine nitrites reflect the presence of bacteria, which reduce urinary nitrates. In the setting of suggestive symptoms, these dipstick results may be enough to warrant empiric antibiotic treatment for cystitis in otherwise healthy young women.

On microscopy, the presence of clinically significant pyuria, defined as more than 10 leukocytes per cubic millimeter, suggests active infection and should prompt empiric therapy in a patient with suggestive symptoms. Microscopic evaluation can detect bacteria in the urine but is not diagnostic, as false positives can occur due to unsterile collection technique.

A urine culture should be performed to confirm the diagnosis, identify the pathogen, and determine its antibiotic susceptibilities. Infection is probable if culture yields more than 10^5 colony forming units (CFUs) per milliliter (mL) of a voided sample, or 10^4 CFUs/mL of a collected sample (i.e., with a catheter). Some women may have symptoms of cystitis and pyuria, but with either low bacterial titers or no growth on cultures. Urethritis from other causes should be considered in these cases, such as infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Imaging is generally not required in patients with acute uncomplicated cystitis, but ultrasonography or computed tomography may be pursued in those suspected of having complicated disease or anatomic abnormalities.

TREATMENT

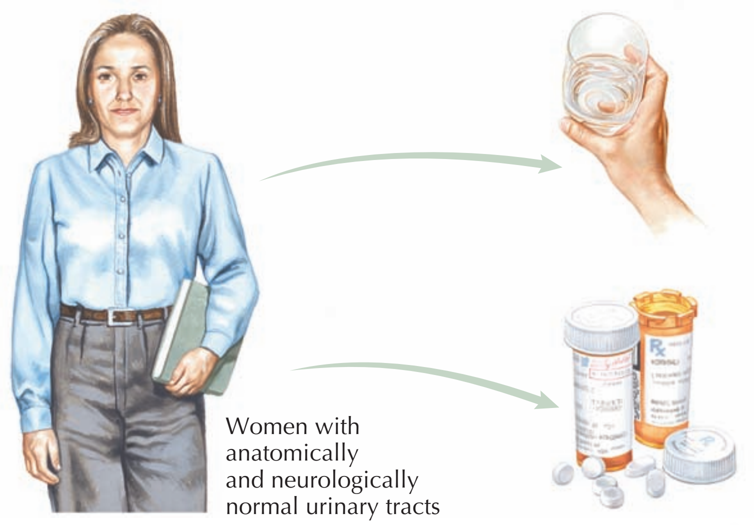
In cases of uncomplicated cystitis, the Infectious Diseases Society of America recommends empiric treatment with trimethoprim-sulfamethoxazole (TMP-SMX). A 3-day course is often adequate. A 5-day course of nitrofurantoin is another acceptable first-line treatment. In certain areas of the United States, where there is concern for resistant *E. coli*, a fluoroquinolone may be considered as the initial agent of choice. Among fluoroquinolones, ciprofloxacin has been shown to have the highest efficacy in short courses. Other drugs that may be used include cephalosporins, amoxicillin with clavulanic acid, and tetracyclines. If the patient has a history of prior infections, susceptibilities on prior cultures should be examined before choosing the initial treatment.

When initiating treatment, rapid hydration of the patient can increase urine production and facilitate clearance of some bacteria through voiding. As discussed earlier, urinary pH plays an integral role in the innate antibacterial activity of urine. Ingestion of cranberry juice (in large quantities) can acidify the urine because cranberries contain precursors of hippuric acid, a weak organic acid. Hence, urine becomes a less hospitable medium for bacterial overgrowth, helping prevent both extension of current infection and future bacterial overgrowth.

In complicated infections, the duration and choice of therapy depend on the population in question.

TREATMENT OF CYSTITIS

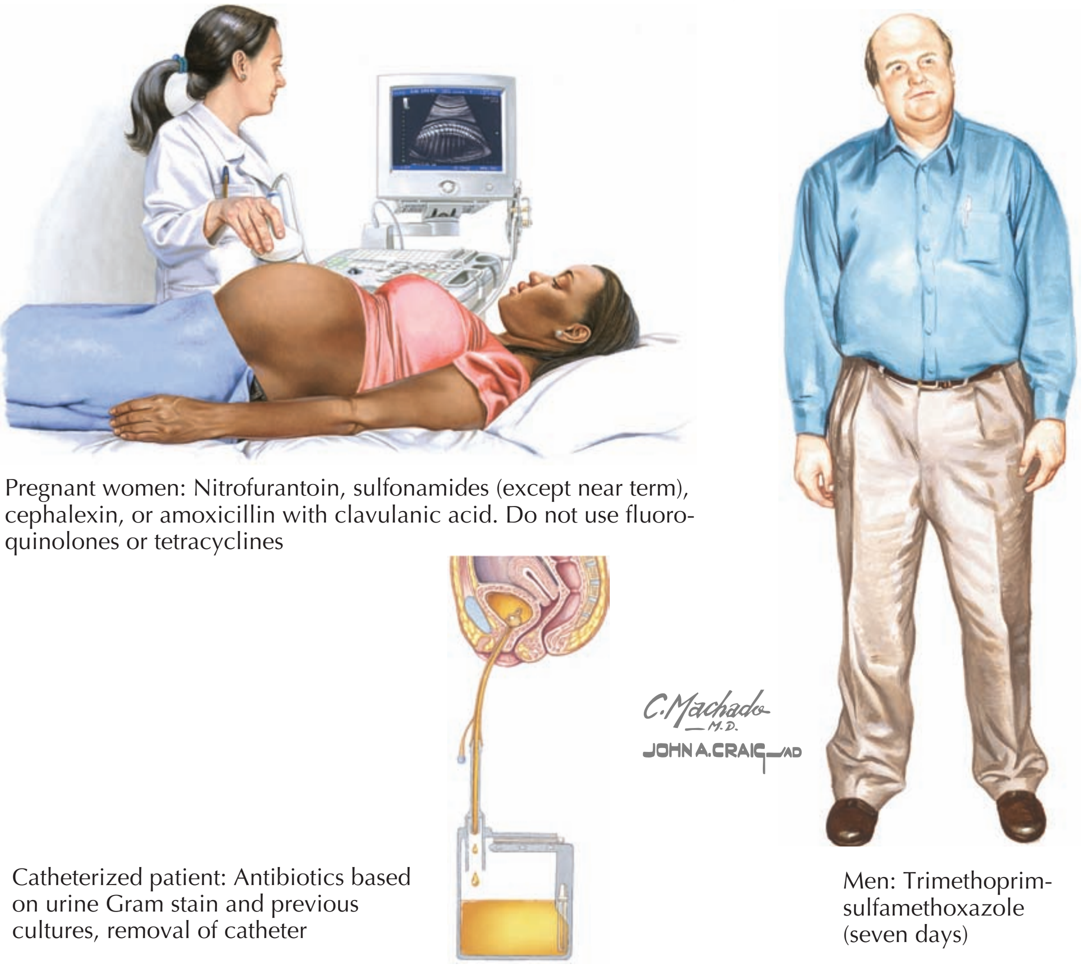
Uncomplicated cystitis


Hydration

Trimethoprim-sulfamethoxazole (three days) or nitrofurantoin (five days)

Women with anatomically and neurologically normal urinary tracts

Complicated cystitis


Pregnant women: Nitrofurantoin, sulfonamides (except near term), cephalexin, or amoxicillin with clavulanic acid. Do not use fluoroquinolones or tetracyclines

Catheterized patient: Antibiotics based on urine Gram stain and previous cultures, removal of catheter

Men: Trimethoprim-sulfamethoxazole (seven days)

CYSTITIS *(Continued)*

For pregnant women, nitrofurantoin, sulfonamides, cephalexin, and amoxicillin with clavulanic acid should be considered, although sulfonamides should not be used near term. Fluoroquinolones and tetracyclines are classified as class C drugs for pregnant women because of their teratogenic effects. The duration of treatment for a lower UTI in a pregnant woman ranges from 3 to 7 days, with shorter courses favored to minimize antibiotic exposure.

In young ambulatory men, the presence of UTI should raise suspicion for anatomic anomalies and may prompt further evaluation with imaging studies. In older men, UTIs may occur in the setting of prostatic disease or catheterization. The choice of antibiotics for men is similar to women, but the duration of therapy should be extended to 7 to 10 days.

For chronically catheterized patients or residents of long-term facilities, the choice of an initial antibiotic agent should be based on local patterns of resistance, including susceptibility data from prior infections. Initial agents may include β-lactams or later generation cephalosporins, such as ceftriaxone or cefepime. If a UTI occurs in the presence of a urinary catheter, the catheter must be removed or changed.

Antibiotic therapy should be adjusted after cultures reveal sensitivities. In high-risk populations, including pregnant women and children, a repeat urinalysis and urine culture should be performed 2 weeks after the completion of the antibiotic course to document clearance of the infection. Low-grade bacteriuria may persist after treatment and may represent colonization in a patient who has otherwise shown clinical improvement (see Plate 5-7).

PROGNOSIS

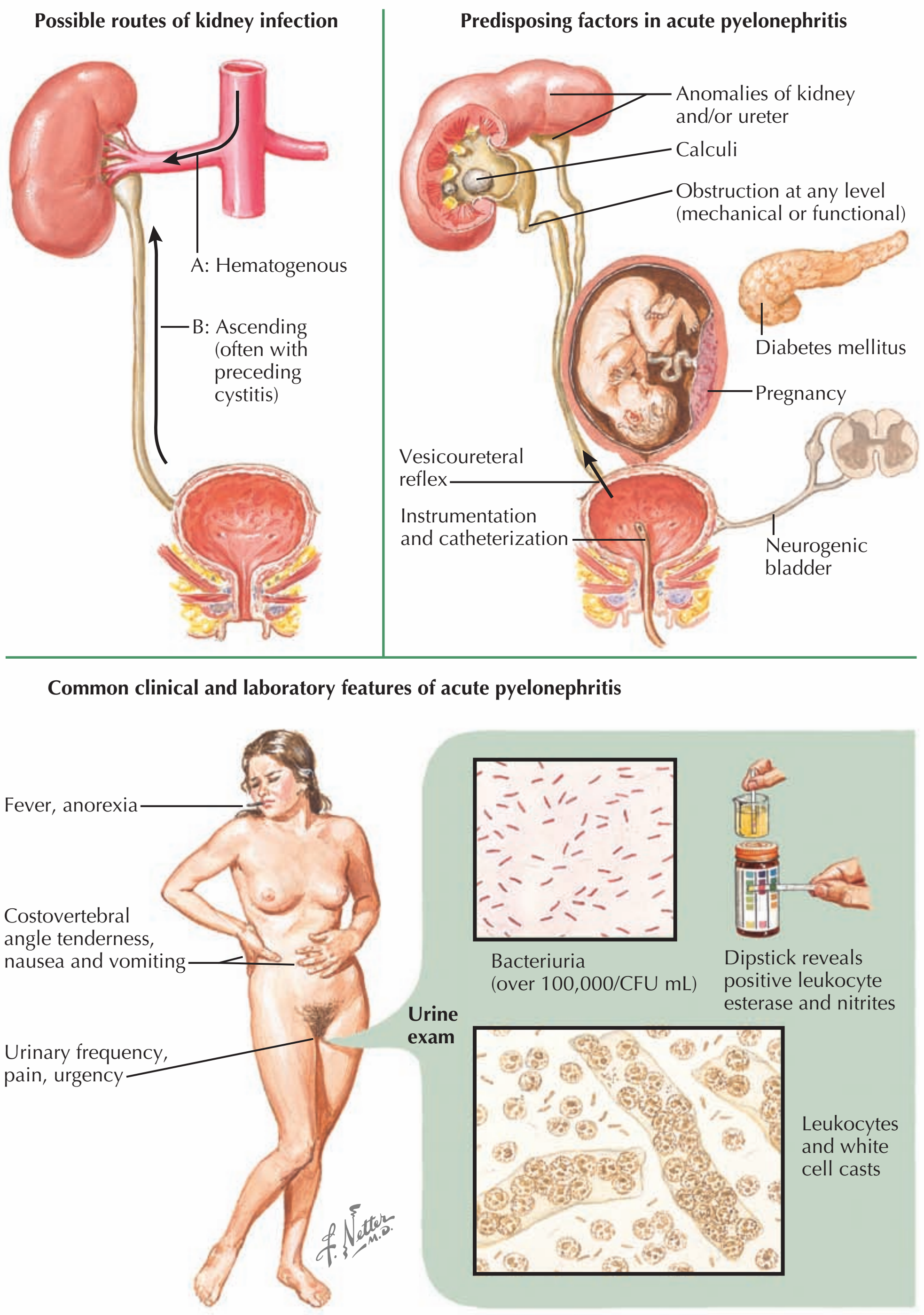
The prognosis of cystitis is usually excellent, but recurrent UTIs are common. Women who experience a UTI have at least a 20% probability of developing another one within 6 months.

UTI recurrence may be attributable to either relapse or reinfection. A relapse occurs 1 to 2 weeks after completion of treatment and involves the same pathogen responsible for the initial disease. Relapse indicates inadequate treatment, undiagnosed upper tract infection, or obstructive disease such as renal calculi or, in men, prostatic enlargement. Patients may need up to 2 weeks of antibiotics. Those with a second symptomatic relapse warrant a repeat course of antibiotics for 2 to 6 weeks, depending on the pathogen and its susceptibilities. Patients with relapsing disease should be evaluated for possible predisposing factors.

A reinfection can also occur shortly after initial therapy. Unlike in relapse, however, the causative organism may be different in the second episode. Reinfection is especially common in cases where there are ongoing niduses of infection, such as urinary catheters with established biofilms. The management strategies are the same as those outlined above for first-time episodes. The source of infection should be identified and eliminated if possible.

Some patients will require prophylactic treatment to prevent recurrent infection. Some young women, for example, experience frequent UTIs associated with sexual intercourse. These patients should be advised to void after sexual activity and can be prescribed antibiotics for single-dose postcoital chemoprophylaxis. Trimethoprim-sulfamethoxazole, nitrofurantoin, or ciprofloxacin can be used in this setting. In postmenopausal women, use of intravaginal estriol cream has been shown to decrease the recurrence of UTIs. Other nonspecific therapies, such as hydration and maintenance of an acidic urine pH, are also reasonable options.

PYELONEPHRITIS



Risk Factors and Major Findings of Pyelonephritis

Possible routes of kidney infection
A: Hematogenous
B: Ascending (often with preceding cystitis)
Predisposing factors in acute pyelonephritis
Anomalies of kidney and/or ureter
Calculi
Obstruction at any level (mechanical or functional)
Diabetes mellitus
Pregnancy
Vesicoureteral reflex
Instrumentation and catheterization
Neurogenic bladder
Common clinical and laboratory features of acute pyelonephritis
Fever, anorexia
Costovertebral angle tenderness, nausea and vomiting
Urinary frequency, pain, urgency
Urine exam
Bacteriuria (over 100,000/CFU mL)
Dipstick reveals positive leukocyte esterase and nitrites
Leukocytes and white cell casts
F. Netter M.D.

Pyelonephritis refers to an infection of the urinary tract that involves the renal pelvis and parenchyma. The condition is more common in women, for whom annual incidence is 12 to 13 per 10,000, than in men, for whom the incidence is 2 to 3 per 10,000 men. It can lead to severe and life-threatening systemic infections (urosepsis) and, if chronic, permanent scarring of renal tissue. It can also be complicated by hemorrhage, abscess formation, and gas formation.

PATHOPHYSIOLOGY

Ascension of pathogens from the lower tract is the most common mechanism of infection, and in many cases cystitis precedes pyelonephritis. The responsible pathogens, and their relative frequencies, are the same as in cystitis (see Plate 5-1). Many of the risk factors are also similar.

In rarer cases, the kidney may be hematogenously seeded in the setting of bacteremia, usually with gram-positive organisms (i.e., *Staphylococcus aureus*).

As with cystitis, the risk of pyelonephritis depends on both host and bacterial factors. In young women, frequency of sexual activity has been associated with a higher incidence of pyelonephritis, presumably because of increased contamination of the lower urinary tract with enteric flora. Diabetics are three times more likely than non-diabetics to develop pyelonephritis during a lower tract infection because of numerous factors. Pregnant women are also at increased risk because of relaxation of smooth muscle around the ureters, which facilitates ascension of infected urine from the lower tract as well as deficiencies in certain aspects of the normal immune response. Patients with nephrolithiasis may have stones that become seeded with bacteria, which make the bacteria very difficult to clear.

Individuals with vesicoureteral reflux (VUR) have multiple factors that render them susceptible to pyelonephritis. First, the retrograde flow of urine from the bladder into the ureters facilitates bacterial ascension. Second, high-grade reflux into the ureters during voiding can cause incomplete bladder emptying and urinary stasis. Third, chronic reflux may cause upper tract scarring, which alters local antiadherence mechanisms. Fourth, those with reflux are more likely to undergo catheterization and instrumentation, which promote colonization of the urinary tract. Finally, lower tract infections may themselves increase the degree of reflux because of the increased intracystic pressure associated with inflammation. Thus individuals with vesicoureteral reflux (VUR) often experience chronic pyelonephritis during childhood, which can lead to renal scarring if severe and untreated.

Several factors determine whether a given pathogen is likely to establish upper tract infection. *E. coli* with type 1 and P fimbriae, for example, are more capable of adhering to the urothelium, which facilitates ascension to the renal parenchyma. These mechanisms are particularly important for pathogens causing pyelonephritis in anatomically normal urinary tracts.

As bacteria infect the upper tract, an inflammatory response occurs in the renal interstitium, where large numbers of leukocytes (predominantly neutrophils in the acute phase) may be seen. Tubular injury, suppurative necrosis, and abscess formation may occur. Even with extensive inflammation, however, the glomeruli and local vasculature generally remain intact. Neutrophils and proteinaceous material are flushed out in the urine as casts. Grossly, the kidney appears enlarged, with multiple, discrete, small surface abscesses.

PRESENTATION AND DIAGNOSIS

In addition to the symptoms associated with cystitis (see Plate 5-2), which may or may not be present, acute pyelonephritis features high fever, anorexia, nausea/vomiting, costovertebral angle tenderness, and flank, abdominal, or pelvic pain. Patients with severe disease may have concurrent septic shock and multiorgan failure. Older patients may have altered mental status. Acute kidney injury does not usually occur in pyelonephritis unless there is concomitant obstruction or shock.

As in cystitis, urinalysis should be positive for leukocyte esterase, indicating the presence of white blood cells, and nitrites, indicating the presence of bacteria. Proteinuria (of up to 2 g/day) may also be noted. On urine microscopy, white blood cell casts may be seen in addition to white blood cells and bacteria.

A complete blood count with differential may reveal leukocytosis with neutrophilia. In some cases, serum chemistries may reveal azotemia or electrolyte abnormalities secondary to dehydration.

Urine culture and at least two sets of blood cultures should be obtained before initiation of antibiotic therapy to determine if there is concurrent bacteremia.

In the absence of acute kidney injury or urinary tract obstruction, radiologic studies do not need to be

PYELONEPHRITIS *(Continued)*

pursued at the outset. In patients who fail to defervesce after 48 to 72 hours of treatment with appropriate antibiotics, however, a renal ultrasound or computed tomography (CT) scan of the abdomen and pelvis may be performed. In uncomplicated pyelonephritis, ultrasonography is usually normal, whereas a CT scan may reveal perinephric stranding and patchy areas of diminished, inhomogeneous enhancement. The presence of an abscess, gas collection, or obstruction indicates complicated pyelonephritis.

TREATMENT

Patients with pyelonephritis should be admitted for intravenous antibiotics if their symptoms are severe or they are unable to comply with oral treatment. For example, a toxic-appearing patient with high fevers, shaking chills, and rigors should be admitted. Patients who are pregnant or immunocompromised should also be admitted. Otherwise, patients can often be managed in an outpatient setting.

For patients being treated on an outpatient basis, fluoroquinolones are appropriate empiric treatment. In patients with drug allergies or a high likelihood of infection with resistant agents, oral third-generation cephalosporins, such as cefpodoxime, may also be considered. Patients should be advised to maintain adequate fluid intake and follow up closely until symptoms resolve.

For patients who require hospitalization and intravenous antibiotics, appropriate empiric therapies include ceftriaxone (a third-generation cephalosporin) or, in areas of low resistance, fluoroquinolones. Fluid resuscitation is also critical. The antibiotic regimen can be refined once culture results clarify the organism's sensitivities.

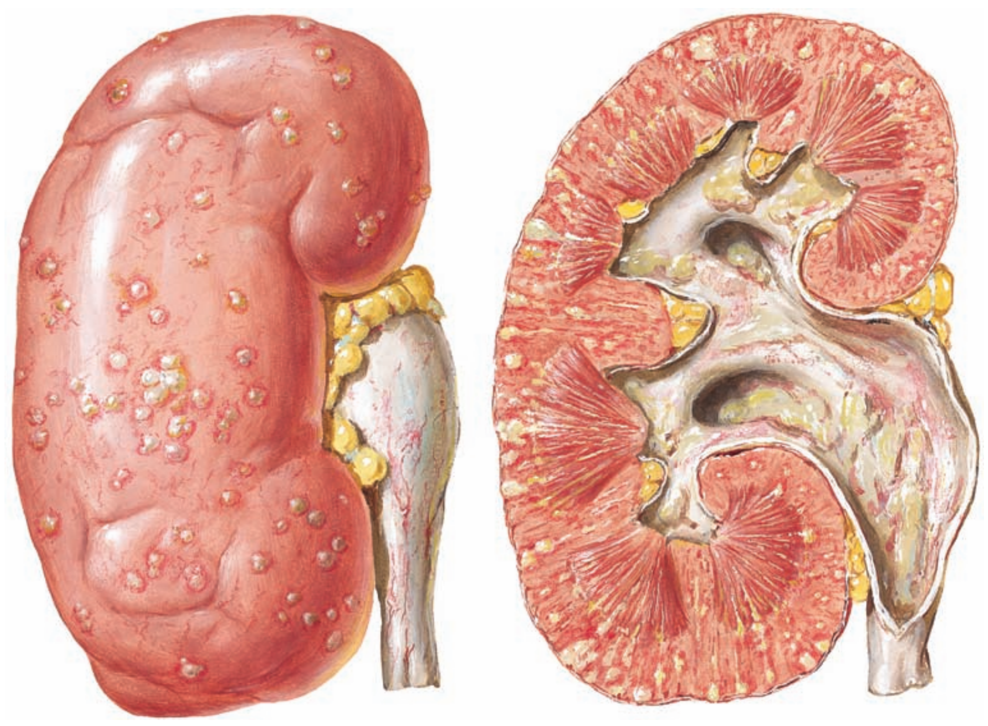
Empiric treatment should be more aggressive for patients with urosepsis or a high risk of being colonized with drug-resistant organisms, such as residents of long-term care facilities or those with a history of frequent hospitalizations. In such cases, initial treatment should employ a broad-spectrum antibiotic, such as piperacillin-tazobactam, ampicillin-sulbactam, or cefepime. Pending culture results, clinicians may wish to add a second agent with additional gram-negative coverage, such as an aminoglycoside or fluoroquinolone. The double coverage strategy provides the highest chances of providing an agent that is active against the causative organism; however, patients should be carefully monitored for renal toxicity and other adverse effects, especially if they are elderly.

In hospitalized patients, pyelonephritis should be treated for 7 to 14 days, depending on severity. It is advisable to obtain a repeat urine culture 5 to 9 days after the completion of treatment, since a subset of patients will experience relapse, possibly without symptoms. Patients with positive repeat cultures should undergo an additional 2 to 4 weeks of treatment and may require evaluation for the presence of an infectious focus, such as an abscess or an infected stone.

PROGNOSIS

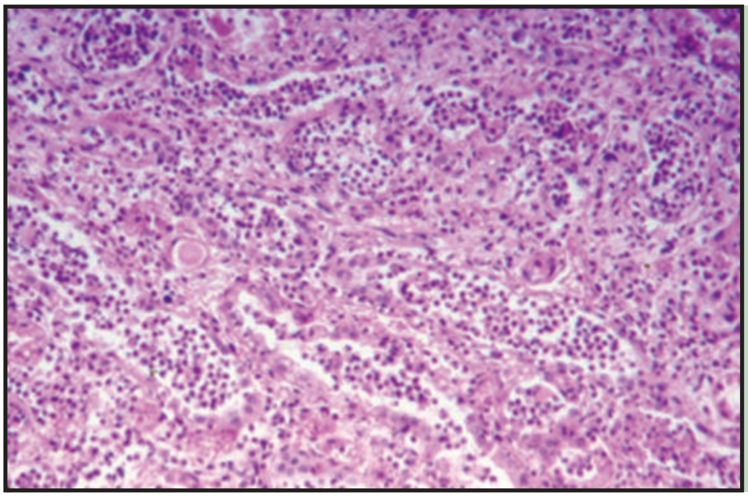
The prognosis of uncomplicated pyelonephritis is excellent unless urosepsis occurs, in which case mortality rates are substantially higher. Moreover, in patients with chronic renal disease or renal scars from childhood pyelonephritis, acute pyelonephritis may lead to further deterioration of renal function. Poor prognosis is also associated with older age, underlying comorbidities, and infection with resistant gram-negative pathogens.

PATHOLOGY OF ACUTE PYELONEPHRITIS



Surface aspect of kidney: Multiple minute abscesses (surface may appear relatively normal in some cases)

Cut section: Radiating yellowish gray streaks in pyramids and minute abscesses in cortex



Acute pyelonephritis with exudate chiefly composed of neutrophils in interstitium and collecting tubules

COMPLICATED PYELONEPHRITIS

Emphysematous pyelonephritis (EPN) is an uncommon but life-threatening necrotizing infection that causes gas formation in the collecting system and renal parenchyma. It is most common in diabetic patients with poor glycemic control.

EPN can occur secondary to *E. coli* or *Klebsiella* spp. Less commonly, *Proteus*, *Pseudomonas*, and *Clostridium* species may be responsible. Gas accumulation occurs in tissues with rapid catabolism where efficient transport of the end products is not present. In diabetes, heavy glycosylation of peripheral vessel walls can produce this effect because of poor circulation.

In addition to the typical symptoms of pyelonephritis described above, patients with EPN can have shock, altered sensorium, thrombocytopenia, and dyspnea. X-ray and CT scans may be notable for the presence of extraluminal gas in the renal tissue and perirenal space.

Nephrectomy is generally the treatment of choice; however, it may not be possible in the setting of decreased renal function, thrombocytopenia, hemodynamic instability, or altered mental status. In these situations, a conservative approach may be pursued, including percutaneous drainage and antibiotic therapy.

Xanthogranulomatous pyelonephritis is another rare form of complicated pyelonephritis, in which the kidney undergoes wide destruction, with the damaged parenchyma replaced by lipid-laden macrophages in granulomatous tissue.

BACTERIURIA

Bacteriuria is defined as the presence of bacteria in uncontaminated urine. Bacteriuria can be associated with a symptomatic urinary tract infection or can simply reflect asymptomatic colonization. In the latter case, the significance and management depends on the patient population.

The presence of bacteria in urine can be established based on positive nitrite dipstick or culture. A clinically relevant degree of bacteriuria is defined as the growth of more than 10^5 colony-forming units (CFUs) of bacteria per milliliter on urine culture. The presence of white blood cells in the urine, as indicated by either positive leukocyte esterase on dipstick or direct visualization on microscopy, suggests infection rather than mere colonization.

The prevalence of asymptomatic bacteriuria among young, nonpregnant women is 1% to 3%. The prevalence is higher among pregnant women, elderly patients, residents of long-term care facilities, and patients with conditions requiring frequent self-catheterization or chronic indwelling urinary catheters. Bacteriuria is much less common in men (<0.1%) but increases with age, likely because of prostatic disease and consequent urinary retention.

MANAGEMENT

The appropriate management of asymptomatic bacteriuria depends on patient characteristics.

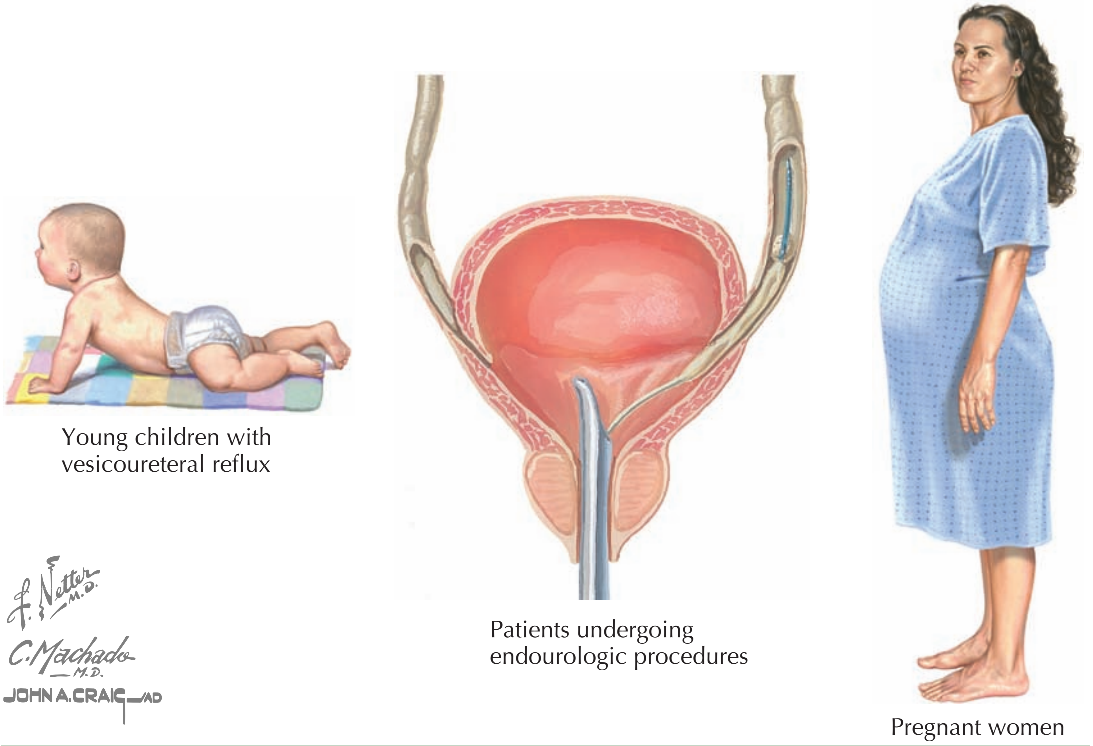
In young children, asymptomatic bacteriuria in the setting of vesicoureteral reflux can lead to renal scarring and even failure. Thus patients with known reflux (see Plate 2-21) are often maintained on antibiotic prophylaxis until the reflux spontaneously improves or a definitive surgical intervention is performed. In healthy children without known reflux, general screening for or treatment of bacteriuria is not recommended.

In pregnant women, asymptomatic bacteriuria increases the risk of pyelonephritis, likely because of relaxation of smooth muscle around the ureters. As such, treatment of asymptomatic bacteriuria has been shown to decrease the likelihood of pyelonephritis from 20%-35% to less than 4%. Moreover, treatment lowers the probability of preterm labor and low birth weight. The current recommendation is to screen pregnant women by performing a urine culture around week 16 of gestation. The optimal frequency of screening is not known. If necessary, antimicrobial therapy should be instituted for 3 to 7 days.

In patients scheduled to undergo endourologic procedures that may injure the urinary mucosal, screening and treatment of bacteriuria is recommended. If necessary, treatment should begin just before the procedure. Treatment does not need to continue postoperatively unless a catheter is to remain in place.

MANAGEMENT OF ASYMPTOMATIC BACTERIURIA

Patients who should be treated



Young children with vesicoureteral reflux

Patients undergoing endourologic procedures

Pregnant women

Patients who generally do not need to be treated

Non-pregnant women (including diabetics)

Men (including diabetics)

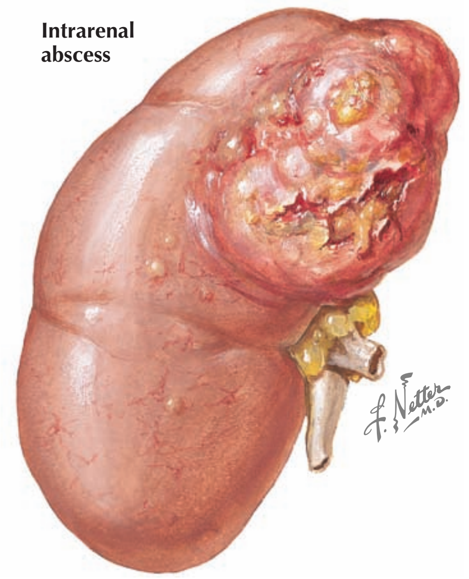
Elderly individuals residing in the community or in long-term care facilities

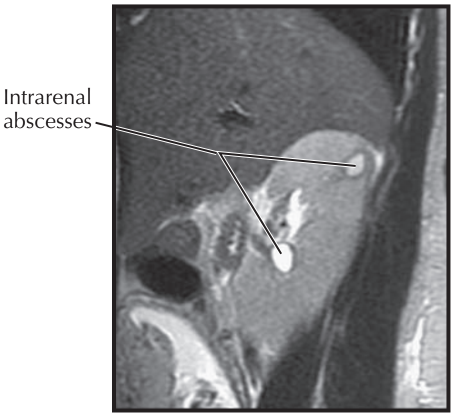
Patients with chronic indwelling catheters

In nonpregnant women, asymptomatic bacteriuria increases the risk of cystitis, but neither general screening nor treatment is recommended because bacteriuria tends to rapidly recur. Likewise, there is no benefit to general screening or treatment of asymptomatic bacteriuria in men. In diabetic patients, treating asymptomatic bacteriuria has not been shown to decrease or delay future urinary tract infections. Similarly, in elderly individuals residing in long-term care facilities, the treatment of asymptomatic bacteriuria has failed to show benefits. In patients with chronic indwelling catheters, research comparing treatment with a placebo has shown no difference in infection rates and demonstrated higher rates of antibiotic resistance among patients receiving treatment.

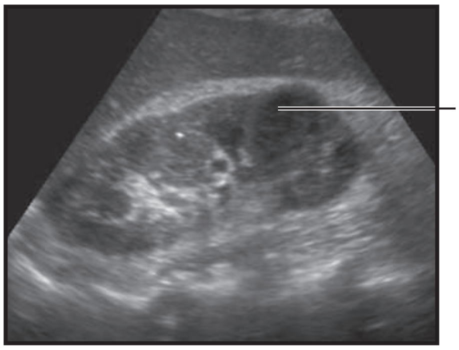
INTRARENAL AND PERINEPHRIC ABSCESSES

Kidney abscesses can be located either within the renal parenchyma (intrarenal abscess) or between the renal capsule and renal fascia (perinephric abscess). Intrarenal abscesses may be present in the cortex or medulla. Perinephric abscesses are generally confined to the renal fascia but may extend into the retroperitoneum.

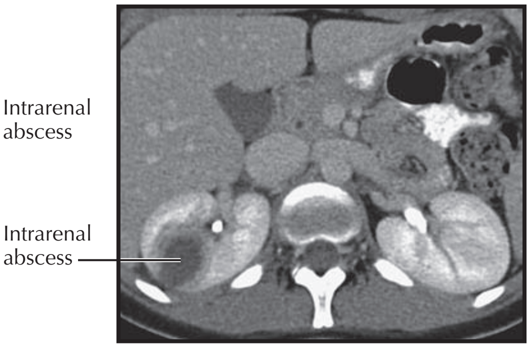




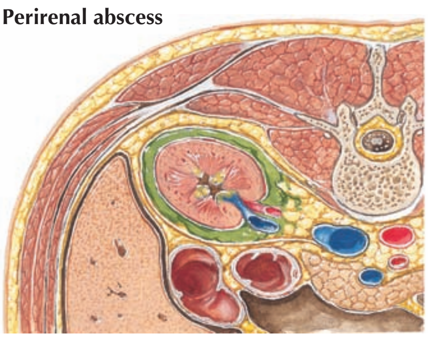
MRI of intrarenal abscesses. T2-weighted sagittal view shows abscesses to be filled with fluid and to have walls distinct from normal kidney.

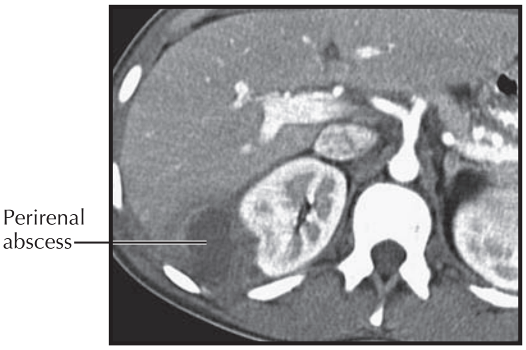


Ultrasound of intrarenal abscess, which appears hypoechoic, has moderately thick wall, and bulges beyond the renal margin.



CT (contrast-enhanced) of intrarenal abscess. Pus in the center is lucent. There is a thick, partially enhancing wall.





CT (contrast-enhanced) of perirenal abscess. Pus in the center is lucent. There is a faintly enhancing wall.

PATHOPHYSIOLOGY

The most common cause of both intrarenal and perinephric abscesses is ascending pyelonephritis in the presence of a urinary tract obstruction. The flushing effect of urine plays an important role in the clearance of bacteria. Hence, an obstruction to the flow of urine with subsequent urinary stasis produces a milieu favorable to infection. In addition, the forniceal rupture that can occur secondary to obstruction can release infected urine into the perinephric space. These infections typically involve gram-negative pathogens (such as *E. coli*, *Klebsiella*, *Pseudomonas*), although polymicrobial infections are also seen and may involve fungal organisms such as *Candida* spp.

A smaller number of abscesses result from hematogenous seeding of the renal parenchyma in the setting of systemic bacteremia. In these cases, the abscesses are typically intrarenal rather than perinephric. In addition, gram-positive organisms (e.g., *Staphylococcus aureus*) are usually responsible.

In both ascending and hematogenous infection, there is tissue necrosis and subsequent sequestration of the phlegmon into an abscess.

PRESENTATION AND DIAGNOSIS

Patients with an intrarenal or perinephric abscess typically have signs and symptoms of acute pyelonephritis (see Plate 5-5) but fail to improve after several days of appropriate antimicrobial therapy (e.g., persistent fever, persistently positive cultures, and no resolution in elevated white blood cell count). In some cases, physical examination may reveal a palpable mass or overlying inflammatory skin changes.

When an abscess is suspected, the basic tests for evaluation of upper UTI should and often already have been performed, including urine and blood cultures. In patients with hematogenously seeded abscesses, a urine culture may reveal organisms not usually found in the urinary tract, such as gram-positive organisms, and the same organism may be identified on a blood culture.

Once an abscess is suspected, abdominal images should be obtained. Computed tomography (CT) is the study of choice, and renal abscesses have the same characteristics as abscesses located elsewhere. The pus-filled central portions are lucent and do not enhance, while the inflamed walls are thicker than those of cysts, have indistinct borders, and do enhance. Ultrasonography may reveal fluid-containing, masslike structures with flow in the walls seen on Doppler imaging.

TREATMENT

Empiric intravenous antibiotic treatment should include broad-spectrum agents that can penetrate walled-off infections. Options include piperacillin-tazobactam, cefepime, and carbapenems. These agents will target gram-negative and most susceptible gram-positive pathogens that can cause an abscess, with the exception of resistant organisms such as methicillin-resistance *Staphylococcus aureus* or vancomycin-resistant *Enterococcus*. The choice of antimicrobial agent can be refined once blood or urine culture results are obtained.

Percutaneous or surgical drainage should be performed for abscesses that are more than 3 to 5 cm in diameter. Gram stain and culture of the aspirate may facilitate identification of the causative pathogen and its susceptibilities. Percutaneous drainage, which can be performed under CT or ultrasound guidance, carries less risk than an open surgical procedure. In the case of a large abscess that cannot be drained with a single aspiration, an indwelling catheter is appropriate. The combination of percutaneous drainage and appropriate antibiotic treatment has been shown to clear more than 90% of infections. When this approach fails, open drainage may become necessary.

The duration of antibiotic therapy depends on the size of the abscess and the extent of drainage. Generally, it is continued for 2 to 3 weeks following successful drainage. The response to antibiotics can be slow, and the patient should be monitored closely for improvement in symptoms and laboratory markers of inflammation, such as leukocyte count, C-reactive protein, and erythrocyte sedimentation rate. Follow-up imaging is recommended after treatment to document resolution, especially in patients with diabetes or other causes of immune compromise.

TUBERCULOSIS

Tuberculosis remains a major infectious disease both worldwide and in the United States. The pathogen responsible for most cases, *Mycobacterium tuberculosis*, infects one third of the world's population, and it is responsible for over 2 million deaths per year. The incidence of this disease is declining in the United States at a rate of approximately 3% to 6% per year; however, tuberculosis remains an important cause of mortality and morbidity among those in immunocompromised states, especially those coinfected with the human immunodeficiency virus (HIV).

Although a majority of those infected with *Mycobacterium tuberculosis* develop disease restricted to the lungs, a recent survey of cases in the United States found that 19% had only extrapulmonary disease, whereas 6% had combined pulmonary and extrapulmonary disease. Of those with extrapulmonary disease, 6.5% had urogenital involvement. In addition, the relative proportion of extrapulmonary cases appears to be increasing: despite a steady decline in the number of new pulmonary tuberculosis cases, there has been little change in the number of new extrapulmonary cases. Worldwide, urogenital involvement is even more common, occurring in up to 40% of extrapulmonary cases. There is evidence, however, that even this number may be an underestimate; in one autopsy study, 73% of patients with pulmonary tuberculosis were found also to have a renal focus.

Urogenital tuberculosis affects men twice as often as women, and the average age at presentation is approximately 40 years old. HIV infection is also a major risk factor not only for active tuberculosis in general, but also for extrapulmonary spread and reactivation.

PATHOPHYSIOLOGY

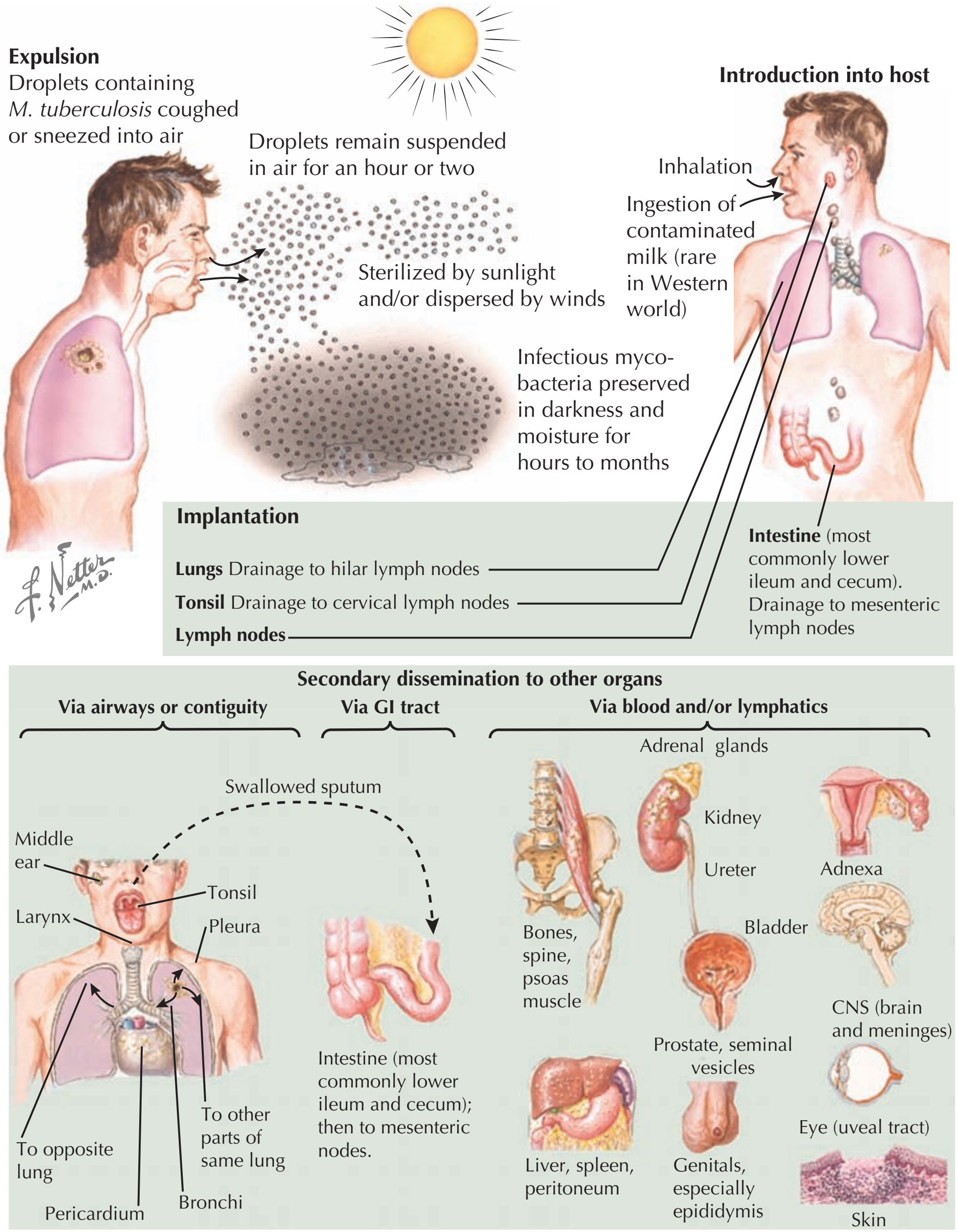
Upon inhalation of airborne bacilli, patients may experience a primary, usually silent, infection that involves formation of granulomas in the pulmonary alveoli. During this initial phase, lymphatic and then hematogenous seeding of distant organs—such as the kidneys and reproductive organs—can occur. In rare instances, wide and uncontrolled dissemination of mycobacteria may lead to miliary tuberculosis, which can also involve the kidneys (see separate section later).

In the urinary system, the renal cortex is the usual site of primary infection. After initial seeding, the disease course is indolent. Indeed, bacilli can remain latent within granulomas for decades or more, both in the kidneys and elsewhere. Reactivation can occur because of a decline in immunity because of age, disease, or malnutrition. Reactivation of renal tuberculosis may lead to further granuloma formation, parenchymal cavitation, papillary necrosis, calcification, and, in rare cases, tuberculous interstitial nephritis.

As the renal disease becomes advanced, it may spread to the rest of the urinary system by direct extension. In the ureter, strictures and calcification may occur. In the bladder, ulceration and fibrosis may occur, leading to wall contraction and a decrease in storage capacity. Fibrosis adjacent to the ureteric orifice may cause it to become retracted and assume a "golf hole" appearance.

Genital disease may occur either because of hematogenous spread or contiguous extension from the urinary system.

TUBERCULOSIS INFECTION AND EXTRAPULMONARY SPREAD


Expulsion
Droplets containing *M. tuberculosis* coughed or sneezed into air
Droplets remain suspended in air for an hour or two
Sterilized by sunlight and/or dispersed by winds
Infectious mycobacteria preserved in darkness and moisture for hours to months
Introduction into host
Inhalation
Ingestion of contaminated milk (rare in Western world)
Implantation
Lungs Drainage to hilar lymph nodes
Tonsil Drainage to cervical lymph nodes
Lymph nodes
Intestine (most commonly lower ileum and cecum). Drainage to mesenteric lymph nodes
F. Netter M.D.
Secondary dissemination to other organs
Via airways or contiguity
Via GI tract
Via blood and/or lymphatics
Swallowed sputum
Middle ear
Larynx
Tonsil
Pleura
To opposite lung
Pericardium
Bronchi
To other parts of same lung
Intestine (most commonly lower ileum and cecum); then to mesenteric nodes.
Adrenal glands
Kidney
Ureter
Bladder
Bones, spine, psoas muscle
Prostate, seminal vesicles
Liver, spleen, peritoneum
Genitals, especially epididymis
Adnexa
CNS (brain and meninges)
Eye (uveal tract)
Skin

PRESENTATION AND DIAGNOSIS

The symptoms of genitourinary tuberculosis can be very nonspecific. Patients often complain of urinary frequency and may, in some cases, experience gross hematuria or flank pain. Some patients may also have constitutional symptoms, including fever and weight loss.

About 90% of patients will have abnormal urinalysis, which may reveal positive leukocyte esterase, hematuria, proteinuria, and low urine pH. About 1 in 10 patients will have only frank hematuria, whereas up to half have microscopic hematuria. As *Mycobacterium tuberculosis* does not convert urinary nitrates, dipstick is often negative for nitrites.

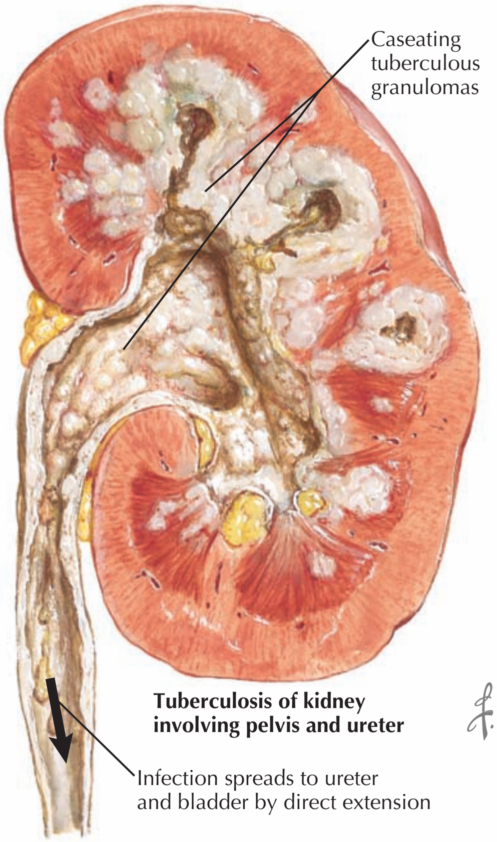
The classic urinary finding—found in up to one quarter of patients—is sterile pyuria, where urine contains numerous white blood cells but no bacterial growth is seen on standard cultures. Of note, bacterial growth does not necessarily rule out renal tuberculosis, since secondary bacterial infection is common.

If sterile pyuria is seen, the differential diagnosis also includes chlamydial urethritis, pelvic inflammatory disease, nephrolithiasis, or renal papillary necrosis. If constitutional symptoms and hematuria are present, a malignancy of the urinary or genital system should also be suspected.

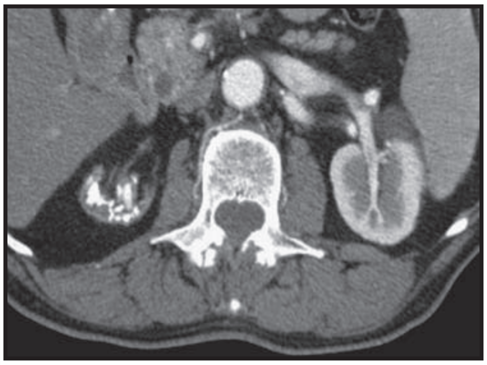
A physician may suspect urogenital tuberculosis if the patient has risk factors for tuberculosis exposure, a history of a positive purified protein derivative (PPD) test, a history of immunocompromise, and constitutional symptoms. It is not uncommon, however, for physicians to prescribe antibacterial treatment at first presentation. A lack of positive urine cultures, no response to antimicrobials, or recurrent episodes of cystitis in the setting of suggestive risk factors should raise a suspicion of mycobacterial infection and prompt further evaluation.

A radiograph may reveal areas of focal calcification in the kidneys and the lower genitourinary tract. Ultrasonography may reveal calcification, hypoechoic renal abscesses, and shrunken kidneys. CT may demonstrate calcifications, renal scarring and cavitation, papillary

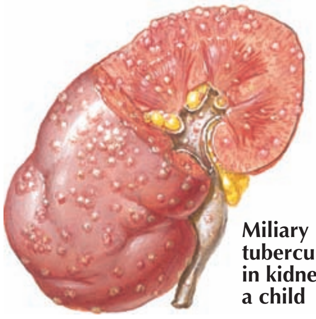
TUBERCULOSIS OF THE URINARY TRACT



Tuberculosis of kidney involving pelvis and ureter

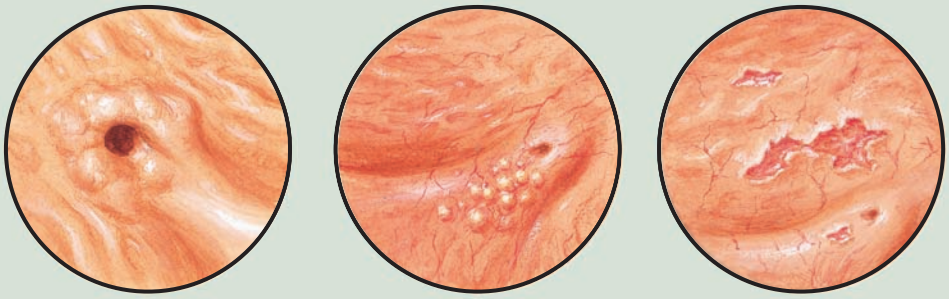


Computed tomography (contrast-enhanced) of advanced right-sided renal tuberculosis reveals marked atrophy and diffuse calcificaton (auto-nephrectomy)



Miliary tuberculosis in kidney of a child

Tuberculosis of bladder, cystoscopic views



Retraction of ureteric orifice ("golf hole" orifice) with fibrosis of surrounding wall

Tubercles in proximity to ureteric orifice

Large and small tuberculous ulcers in urinary bladder

TUBERCULOSIS *(Continued)*

necrosis, strictures of the collecting system, and diminution of renal function. Imaging of the thorax should also be performed to rule out concomitant pulmonary or spinal infection. Many patients will have evidence of prior pulmonary infection, and up to 30% to 40% will be found to have active pulmonary disease.

Once tuberculosis is suspected, the bacillus can be identified in urine by acid-fast staining. Because sensitivity is low, multiple early morning midstream voided specimens are often collected to increase detection power. Culture on either liquid broth or solid Löwenstein-Jensen medium remains the gold standard for diagnosis, and it also has the advantage of providing information about mycobacterial drug susceptibilities.

Although culture sensitivity can be as high as 80%, results can take as long as 6 to 8 weeks. For that reason, polymerase chain reaction (PCR) studies may be performed to detect *M. tuberculosis* in urine earlier in the clinical course. The advantage of this test is not only its high sensitivity (up to 95%), but also its fast turnaround time, with results often obtained within 24 hours.

In situations when there is a high clinical suspicion for tuberculous disease, but microbiologic testing is not definitive, more invasive methods of diagnosis, such as percutaneous tissue biopsy, may be required. Histopathologic examination of the obtained tissue reveals caseating granulomas.

In immunocompetent patients, an intradermal tuberculin test (PPD) can be performed as an additional screen for tuberculosis exposure; however, it is not helpful in diagnosis of the disease because results have been reported as positive in only 60% of patients with urinary tuberculosis. Interpretation of tuberculin test results should follow standard cut-off values: 5 mm or more for immunocompromised patients, 10 mm or more for patients at high risk (inmates, health-care workers, long-term care facility residents, intravenous drug users, and immigrants), and 15 mm or more for patients without any risk factors. A positive tuberculin test result indicates prior exposure but is not diagnostic of active disease. In patients with advanced HIV or other immunocompromising conditions, tuberculin test results may be negative secondary to anergy and should not be used to rule out tuberculosis.

TREATMENT

The treatment of urogenital tuberculosis involves a combination of antituberculous therapy and surgical resection, where possible, of local disease. Consultation with experts should be sought, given not only the complexity of the disease course but also the potential adverse effects associated with treatment.

Pending the return of culture and sensitivities, the patient should be initiated on a four-drug regimen that includes isoniazid, ethambutol, rifampin, and pyrazinamide. If cultures indicate the organism is sensitive to isoniazid, rifampin, and pyrazinamide, the ethambutol can be stopped. After 8 weeks, pyrazinamide is usually stopped, because it has an early bactericidal effect.

The duration of therapy with the remaining two agents depends on the patient's immune status. Therapy may also need to be adjusted if infection occurs in an area with high levels of multidrug-resistant or extensively drug-resistant tuberculosis.

PROGNOSIS

In the developed world, tuberculosis is rarely a cause of chronic kidney disease. Preservation of renal function, however, depends on early detection to limit renal parenchymal destruction. In developing countries, where diagnosis and treatment are more likely to be delayed, permanent loss of renal function is more common.

MILIARY TUBERCULOSIS

In addition to being the site of locally reactivating granulomas, as described previously, the kidneys may rarely be involved in the disseminated disease known as miliary tuberculosis.

Miliary tuberculosis results from widespread hematogenous dissemination of tuberculous bacilli after invasion of the pulmonary circulation. It may occur during the time of primary infection or at reactivation, and it is often associated with the extremes of age and other conditions that compromise the immune system.

Patients have more pronounced constitutional systems and extensive pulmonary disease. Overwhelming systemic illness may overshadow the effects of renal involvement. The workup of miliary tuberculosis includes acid-fast bacillus smears, culture, PCR, and histopathologic examination of affected tissues (e.g., bone marrow, lymph nodes, liver). If the kidney is affected, numerous granulomatous lesions may be present throughout the cortex and, less commonly, the medulla. On microscopic examination these granulomas reveal central caseous necrosis.

Rapid diagnosis of military tuberculosis is essential, and treatment with the combination regimen described above should be promptly initiated.

SCHISTOSOMIASIS

Schistosomiasis is a parasitic infection caused by *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi*, or *S. intercalatum*. Worldwide, more than 207 million people are infected with schistosomes, and 700 million are at risk. The annual mortality is close to 100,000.

As S. *haematobium* is the species most associated with renal and urologic disease, it is the main focus of this section. This parasite is found throughout most of Africa and the Middle East, and humans become infected when exposed to it in fresh water. Because eggs are excreted in human waste, poor sanitation plays an important role in sustaining fresh water reservoirs.

In endemic populations, infection generally occurs during childhood. The prevalence of the disease, as well as the parasite burden, peaks around 15 to 20 years of age. Because infection can occur during even brief exposure, however, travelers to endemic regions are also susceptible.

LIFE CYCLE

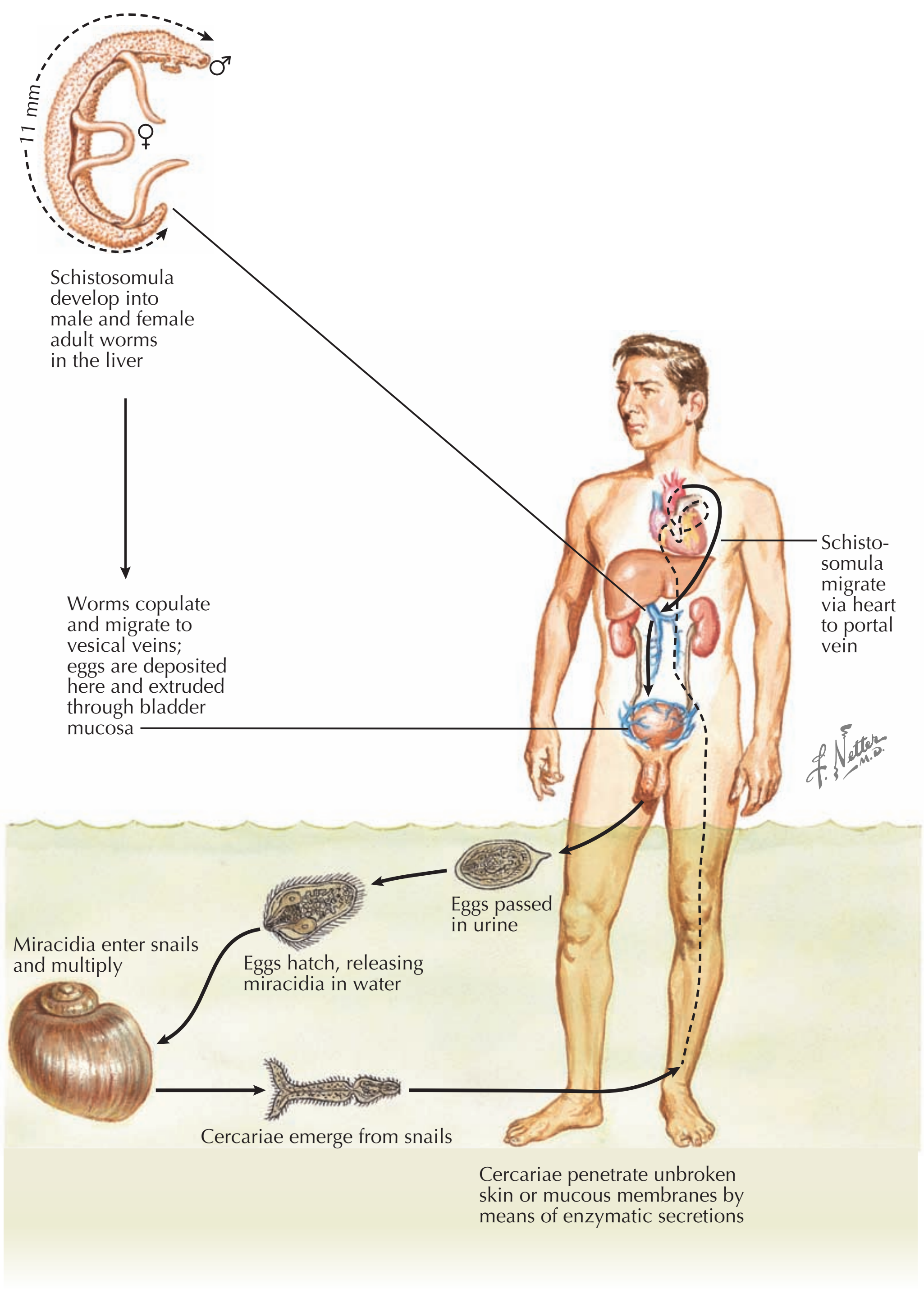
Fresh water snails are the intermediate hosts for the larval forms of *S. hematobium*, whereas humans are the definitive hosts for the adult worms.

Eggs are excreted in the urine of infected humans. The eggs hatch into miracidia larvae upon contact with fresh water and then infect fresh water snails. In this intermediate host, miracidia multiply asexually into sporocysts and later into cercaria larvae. After 6 to 8 weeks, motile cercariae are released back into the water by the thousands. When they come into contact with humans, they penetrate the skin, aided by enzymatic secretions.

Once cercariae have entered the human host, they lose their tails, transform into schistosomula, and travel through the lymph and venous systems to the right side of the heart. They then pass through the pulmonary capillaries and left side of the heart and then travel through the mesenteric vasculature until they reach the portal vein. In the liver, they mature into adult worms over 6 weeks, then migrate through the venous system to the pelvic venous plexus, located around the distal end of the ureter and the bladder. Adult male worms enclose the females in a gynecophoric canal. The average life span of the adult worm is 3 to 5 years, but some worms can live for decades.

Mature female worms produce eggs throughout their lifetime. Eggs are released into the vesical veins, migrate across the bladder wall, and are excreted in urine, completing the life cycle.

LIFE CYCLE OF *SCHISTOSOMA HAEMATOBIUM*


11 mm
♂
♀
Schistosomula develop into male and female adult worms in the liver
Worms copulate and migrate to vesical veins; eggs are deposited here and extruded through bladder mucosa
Schisto-somula migrate via heart to portal vein
F. Netter M.D.
Eggs passed in urine
Eggs hatch, releasing miracidia in water
Miracidia enter snails and multiply
Cercariae emerge from snails
Cercariae penetrate unbroken skin or mucous membranes by means of enzymatic secretions

PATHOPHYSIOLOGY

Adult worms evade the immune system and do not typically produce symptoms.

In contrast, eggs cause irritation and microhemorrhage as they pass through the bladder wall. More importantly, however, egg antigens stimulate the immune system to mount a significant T-cell dependent response.

The granulomatous inflammation that ensues can lead to the formation of large polypoid masses that project into the bladder lumen. The eggs also promote calcification, sometimes involving the entire bladder. If infection is chronic, the resulting inflammation can lead to squamous cell carcinoma of the bladder. As entrapped eggs die and antigenic stimulation ceases, tissue fibrosis occurs, which leads to flat, tan-colored areas of mucosa known as “sandy patches.”

In some cases, these inflammatory processes involve the ureteric orifices or urethra, causing stricture formation and obstruction. These abnormalities may lead to hydronephrosis and, in a small percentage of cases, renal failure. In addition, they increase the risk of recurrent bacterial urinary tract infections.

PRESENTATION

Acute. Shortly after contact with cercariae, a small number of individuals develop local urticaria followed by macular rash. In previously unexposed persons, the rash is usually self-limited and brief. In sensitized individuals, it may develop into a pruritic maculopapular rash that persists for several days.

About 1 to 3 months after schistosomal infection, a small number of previously unexposed individuals may develop a fulminant febrile illness called Katayama fever. The syndrome coincides with the onset of egg production, and it typically causes diarrhea, hepatosplenomegaly, eosinophilia, pulmonary infiltrates, and (in rare cases) central nervous system involvement. Signs and symptoms usually spontaneously resolve after 10 to 12 weeks.

SCHISTOSOMIASIS *(Continued)*

Chronic. Chronic disease becomes evident months or even years after initial infection, and the severity reflects the worm burden.

The most salient features typically are dysuria and gross or microscopic hematuria. If severe, the hematuria may cause anemia. If the ureters or urethra are involved, patients may have symptoms of obstruction (see Plate 6-1).

In many female patients, deposition of the eggs in the genital tract leads to sandy patches, mucosal bleeding, and occasionally ulcerative or nodular lesions of the vulva, perineum, and cervix. In some male patients, hematospermia can result from involvement of the prostate and seminal glands (vesicles).

DIAGNOSIS

The diagnosis should be suspected in any patient with dysuria and hematuria who has a history of travel to endemic areas. In women, a pelvic examination may reveal sandy patches. Up to two thirds of infected patients have nonspecific laboratory abnormalities, such as eosinophilia. A superimposed bacterial urinary tract infection may also be noted.

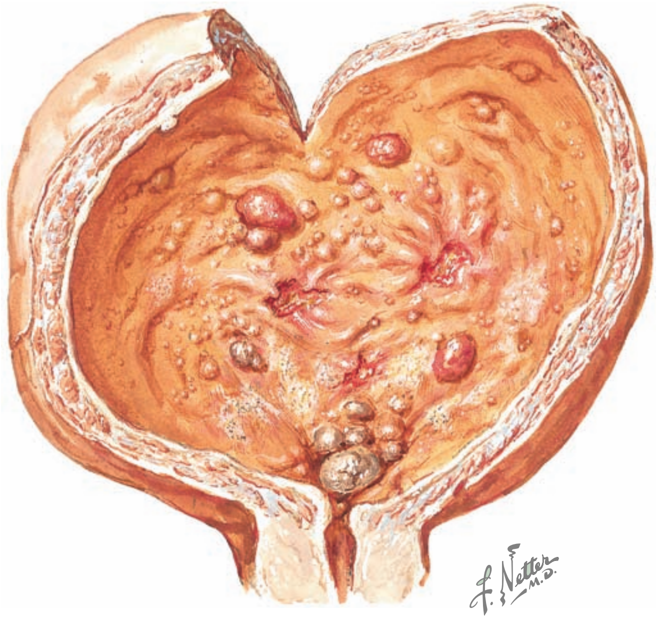
Once *S. haematobium* infection is strongly suspected, definitive diagnosis is accomplished using microscopic examination of the urine to detect eggs, as well as serologic tests to detect the presence of antischistosomal antibodies.

A single urine sample from a patient with light infection may contain few to no eggs. Thus repeated urine examinations are often required. With *S. haematobium* infections, timing the collection of urine samples to midday, when egg excretion is highest, may be helpful. If patients are strongly suspected of having infection but repeated urine samples are negative, biopsy of the bladder mucosa may demonstrate the presence of eggs.

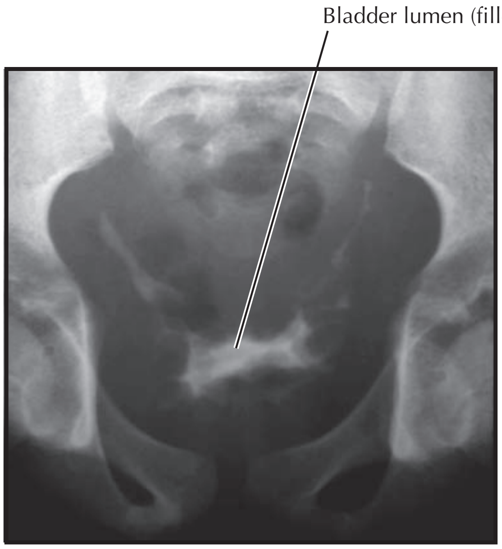
Serologic tests generally have very high sensitivity and specificity, but they may be negative in the acute stage of the disease. The most significant problem with these tests is that they cannot differentiate past from current infections. Thus they are primarily helpful in returning travelers who would not be expected to have preexisting anti-schistosomal antibodies.

Intravenous pyelogram or CT may reveal focal thickening of the bladder wall and polypoid bladder lesions. In more advanced disease, bladder volume may be diminished, and ureteral strictures with resulting hydroureteronephrosis may be seen. The bladder and ureteral walls may appear calcified. Where the disease is endemic, these findings may be pathognomonic for chronic urinary schistosomiasis, but tuberculosis, other kinds of cystitis, and even bladder malignancies may produce bladder wall calcification as well.

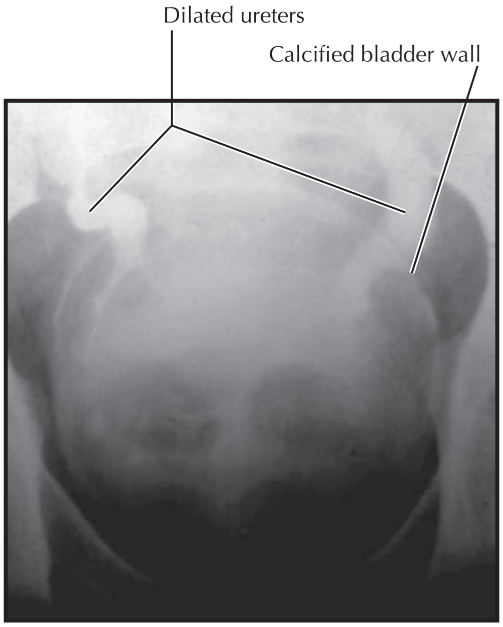
EFFECTS OF CHRONIC *SCHISTOSOMA HAEMATOBIUM* INFECTION



"End-stage" schistosomal bladder: fibrosis and calcification of the bladder wall, numerous papillomas and nodules, sandy patches with pale yellow avascular appearance, chronic ulcers, encrustation, bladder neck, and left ureteral orifice obstructed



Intravenous pyelogram of a patient with chronic schistosomiasis shows a contracted bladder with polypoid filling defects representing focal inflammatory masses.



Intravenous pyelogram of a patient with chronic schistosomiasis shows calcification of the bladder wall and dilation of the ureters secondary to distal strictures.

TREATMENT

Praziquantel is the therapy of choice for all five species of schistosomes. It is relatively well-tolerated and has minimal adverse effects. It has been shown to have an 85% cure rate with first treatment. Patients with residual infection should be retreated. Resistance to this agent is rare but has been reported in some travelers returning with *S. haematobium* infections; however, there are currently no other agents as efficacious as praziquantel for the treatment of schistosomiasis.

Praziquantel has been demonstrated to be safe in pregnancy, and current World Health Organization (WHO) guidelines recommend that symptomatic pregnant woman be treated. Some experts, however, advise delaying treatment until after the first trimester.

Glucocorticosteroids can reduce the inflammation associated with egg release, but they are recommended only in the setting of neurologic disease or in acute infection.

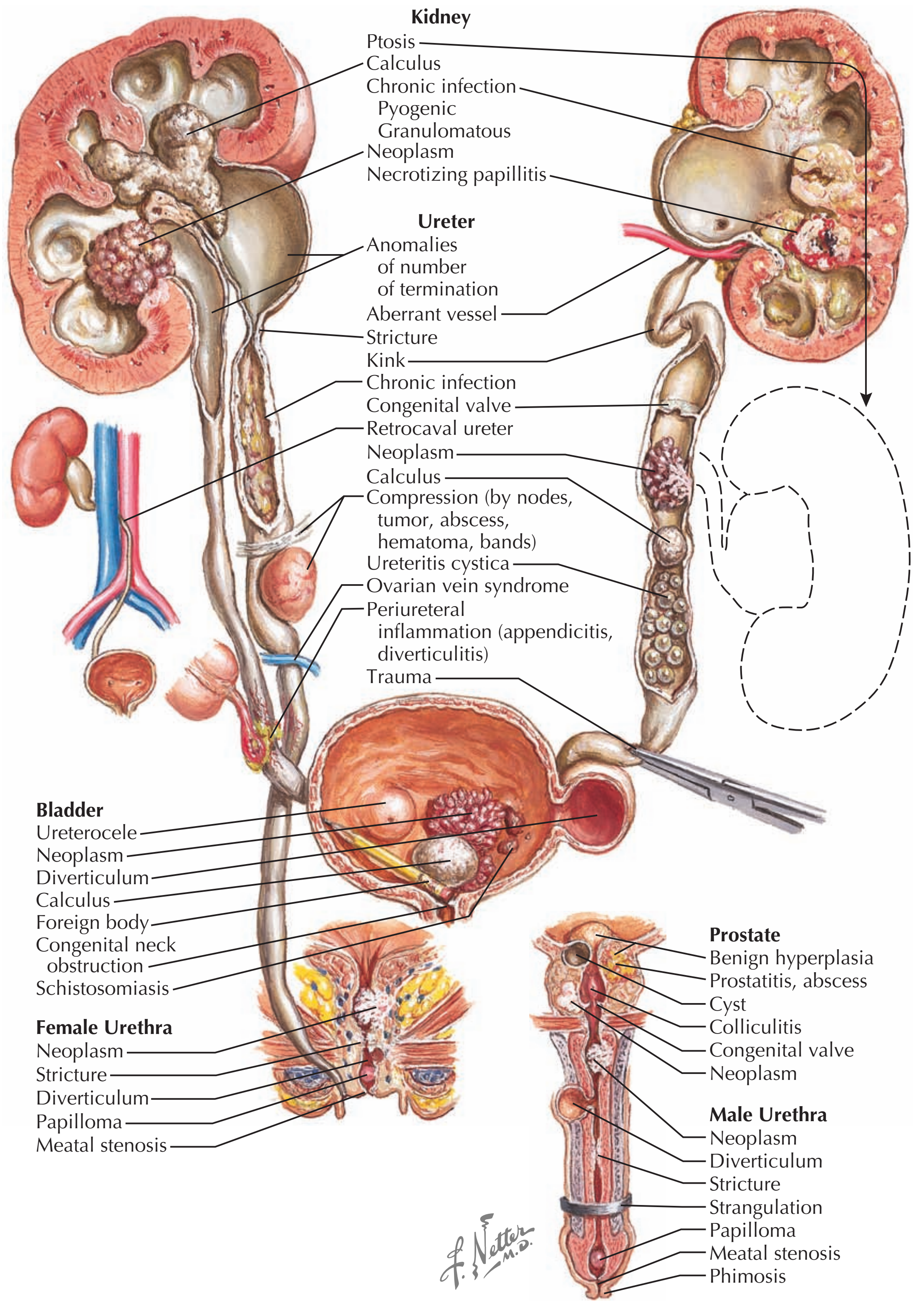
PREVENTION

Travelers should be advised to avoid contact with fresh water reservoirs when visiting endemic areas. When contact does occur, travelers should aggressively dry off with a towel to prevent cercariae from penetrating the skin. Medical evaluation, as outlined above, should be sought upon return home.

Efforts aimed at improving water and sanitation infrastructure in endemic countries may have a significant impact on infection rates. In areas of high prevalence, the WHO recommends regular administration of antischistosomal medications.

SECTION 6

URINARY TRACT OBSTRUCTIONS


Etiology of Obstructive Uropathy
Kidney
Ptosis
Calculus
Chronic infection
Pyogenic
Granulomatous
Neoplasm
Necrotizing papillitis
Ureter
Anomalies
of number
of termination
Aberrant vessel
Stricture
Kink
Chronic infection
Congenital valve
Retrocaval ureter
Neoplasm
Calculus
Compression (by nodes, tumor, abscess, hematoma, bands)
Ureteritis cystica
Ovarian vein syndrome
Periureteral inflammation (appendicitis, diverticulitis)
Trauma
Bladder
Ureterocele
Neoplasm
Diverticulum
Calculus
Foreign body
Congenital neck obstruction
Schistosomiasis
Female Urethra
Neoplasm
Stricture
Diverticulum
Papilloma
Meatal stenosis
Prostate
Benign hyperplasia
Prostatitis, abscess
Cyst
Colliculitis
Congenital valve
Neoplasm
Male Urethra
Neoplasm
Diverticulum
Stricture
Strangulation
Papilloma
Meatal stenosis
Phimosis
F. Netter M.D.

OBSTRUCTIVE UROPATHY

Obstructive uropathy encompasses the numerous sequelae that may be observed when there is an anatomic or functional blockage of the natural flow of urine. Obstructions may occur at any level in the urinary tract, and the clinical signs and symptoms often provide information about both location and severity.

Obstructions may be classified as congenital or acquired, acute or chronic, partial or complete, and intrinsic or extrinsic. All of these characteristics must be taken into consideration when deciding on the optimal treatment plan.

PATHOPHYSIOLOGY

Congenital obstruction may occur secondary to numerous abnormalities in normal urinary tract anatomy, including congenital urethral meatal stenosis, posterior urethral valves (in boys, see Plate 2-34), ureterocele (see Plate 2-26), ectopic ureter (see Plate 2-25), and ureteropelvic junction obstruction (see Plate 6-6). In addition, a congenital spinal dysraphism, such as myelomeningocele or sacral agenesis, may result in bladder dysfunction and functional obstruction.

Acquired obstructions may occur secondary to numerous different phenomena, either intrinsic (i.e., within the ureteral lumen) or extrinsic. In the upper tract (i.e., the kidneys and ureters), the numerous causes of intrinsic obstruction include nephrolithiasis (see Plate 6-3), ureteral strictures (see Plate 6-7), tumors (Plate 9-9), polyps, blood clots, and fungal balls. The numerous causes of extrinsic obstruction include retrocaval ureter (see Plate 2-19), retroperitoneal fibrosis, retroperitoneal hematoma, primary retroperitoneal tumor, pelvic lymphadenopathy, and pregnancy. A functional, rather than structural, obstruction may occur secondary to a nonperistaltic segment of ureter, as seen in some ureteropelvic junction (UPJ) or ureterovesical junction (UVJ) obstructions. In the lower tract (i.e., the bladder and urethra), common causes of intrinsic obstruction include urethral stricture, urethral diverticulum, foreign body, benign prostatic hyperplasia (BPH), prostate cancer, primary bladder neck dysfunction, bladder neck contracture, and bladder cancer. Meanwhile, extrinsic compression may occur secondary to local extension of cancers in adjacent organs (e.g., cervical, uterine). A functional obstruction may result from neuropathic bladder dysfunction (see Plate 8-2).

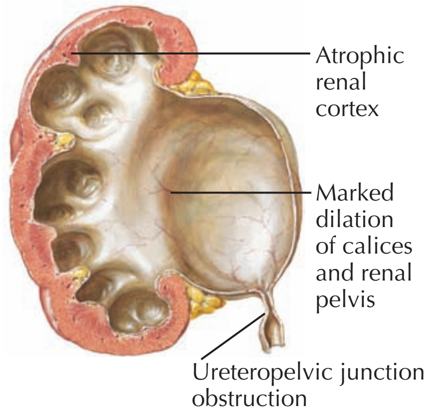
An obstruction has numerous effects on the urinary system, beginning with compensation and ending with symptomatic decompensation.

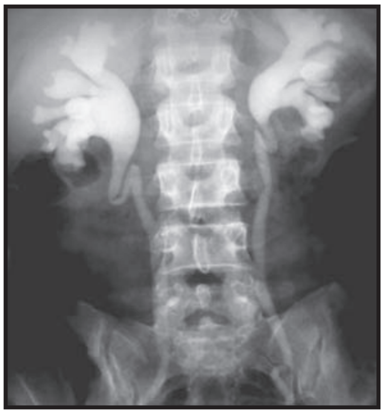
In the upper tract, compensation involves thickening of ureteral smooth muscle to increase the strength of peristaltic waves against the obstruction. In addition, there is dilation proximal to the obstruction, which is called hydronephrosis if it involves the kidney, or hydroureteronephrosis if it involves both the kidney and ureter. The degree of hydronephrosis is determined by the location, degree, and duration of the obstruction. The renal pelvis becomes dilated first, followed by dilation of the calyces. The calyces lose their normal concave shape and become blunted.

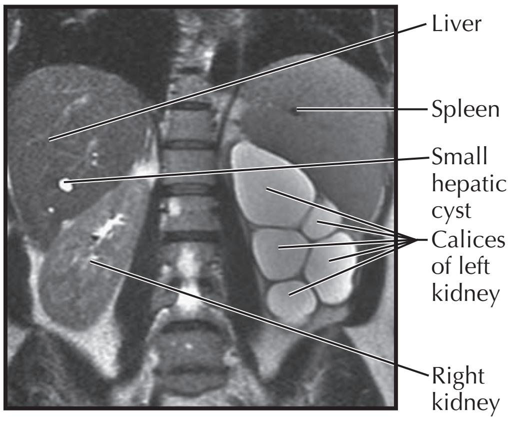
Decompensation occurs as the ureter lengthens and becomes tortuous, followed by replacement of normal ureteral muscle with scar tissue. As a result, the ureter progressively loses its ability to contract and transport a bolus of urine. In the kidney, pressure from the obstruction is ultimately transmitted to the renal tubules, which leads to reflex vasoconstriction and reduction of renal blood flow. The glomerular filtration rate is thus reduced in the obstructed nephrons. If

Sequelae of Urinary Tract Obstruction

Upper tract

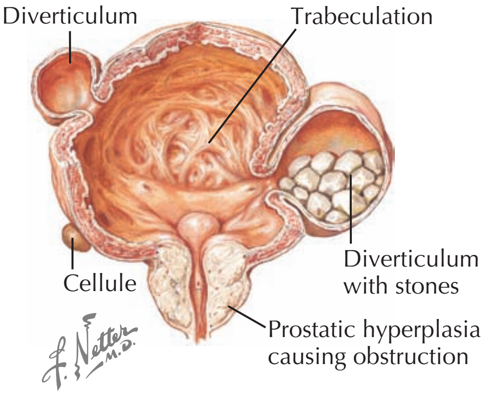

Atrophic renal cortex
Marked dilation of calices and renal pelvis
Ureteropelvic junction obstruction

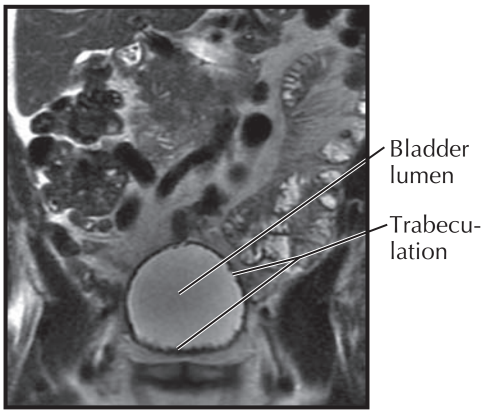

Intravenous pyelogram of bilateral hydroureteronephrosis from bladder outlet obstruction



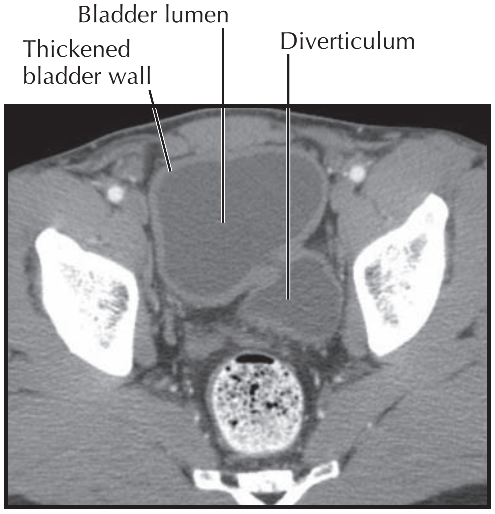
MRI of left-sided hydronephrosis. The urine-filled calyces are markedly dilated, and the renal parenchyma is very thin.

Lower tract





MRI of bladder with outlet obstruction reveals trabeculation.



CT scan of bladder reveals a diverticulum and diffuse thickening of the bladder wall.

OBSTRUCTIVE UROPATHY

(Continued)

bilateral, these changes may be associated with acute kidney injury. In chronic, unrelieved obstruction, there may be irreversible atrophic changes in the renal cortex resulting from chronic ischemia and inflammation.

In the lower tract, compensation involves hypertrophy of the detrusor muscle in an attempt to overcome the obstruction. Chronic hypertrophy, however, can lead to trabeculations, cellules, and diverticula. Trabeculations are interwoven bundles of hypertrophied detrusor muscle that replace the smooth surface of a normal bladder. Cellules are small pockets of mucosa that have herniated between the most superficial strands of detrusor muscle. Diverticula are more pronounced outpouchings that push through all of the detrusor muscle layers. Because there is no contractile force around the walls of diverticula, they are unable to effectively eliminate urine, which may promote formation of bladder stones.

Decompensation occurs as the bladder wall further deteriorates and becomes diffusely replaced with scar tissue. As a result, the bladder is unable to properly contract. The high pressure within the bladder lumen may overwhelm the ureterovesical junctions, causing a secondary reflux that transmits high pressure to the upper tract.

PRESENTATION AND DIAGNOSIS

Numerous symptoms may signal the presence of a urinary tract obstruction. In the upper tract, flank pain may occur secondary to increased stretching of the renal capsule. In the case of an impacted ureteral stone, additional symptoms include hematuria, nausea, and vomiting, as well as systemic symptoms if bacteriuria or bacteremia is present. In the lower tract, outlet obstruction may cause urinary frequency and urgency, low abdominal pain (caused by bladder spasms), and penile/urethral pain in males. Over time, urinary hesitancy and a decrease in the force of the stream may occur as the bladder loses its contractile strength. Finally, complete urinary retention may occur, leading to stasis, infection, bladder stone formation, and overflow incontinence.

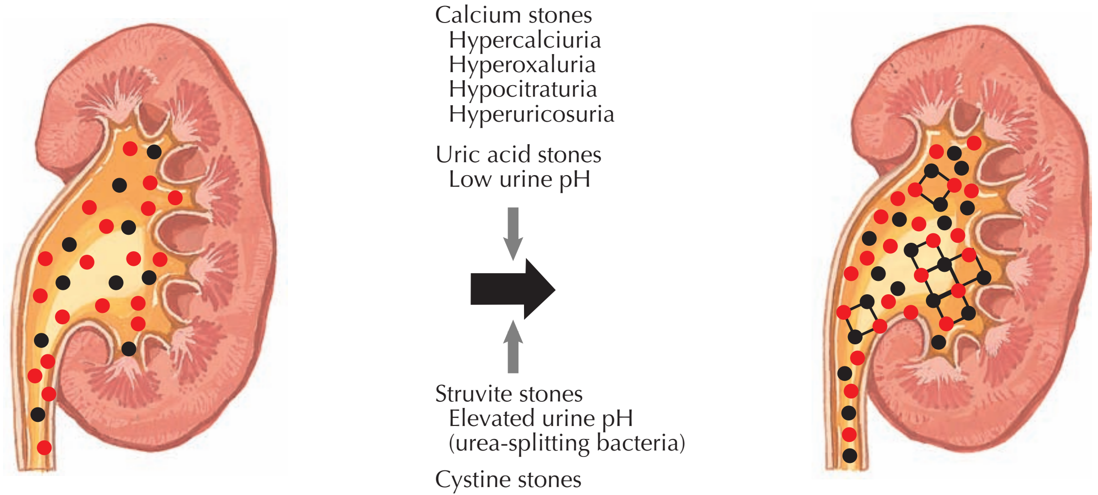
The most important tools for diagnosis are the history and physical examination; however, numerous imaging techniques are often used to confirm and further characterize the obstruction. Nonfunctional imaging studies include non–contrast computed tomography (CT), renal sonography, retrograde pyelogram, retrograde urethrogram, and cystography. These tests can determine the anatomic location of the blockage but cannot assess function. Functional imaging studies include contrast-enhanced CT, radionuclide studies, intravenous pyelography, and urodynamics.

More invasive tests—such as cystoscopy, ureteroscopy, and nephroscopy—allow clinicians to make diagnoses under direct vision and simultaneously perform therapeutic interventions. These tests, however, do not provide any functional information.

Acute decompression of the urinary tract may be accomplished using transient interventions, such as placement of a Foley catheter, suprapubic tube, ureteral stent, or percutaneous nephrostomy tube. Depending on the level and cause of obstruction, definitive therapy may require surgical intervention, such as a transurethral outlet surgery (e.g., urethrotomy, prostate incision or resection), ureteral surgery (e.g., incision, balloon dilation, ureteroscopy), or abdominal surgery (e.g., ureteropelvic junction obstruction repair, removal of retroperitoneal tumor).

UROLITHIASIS

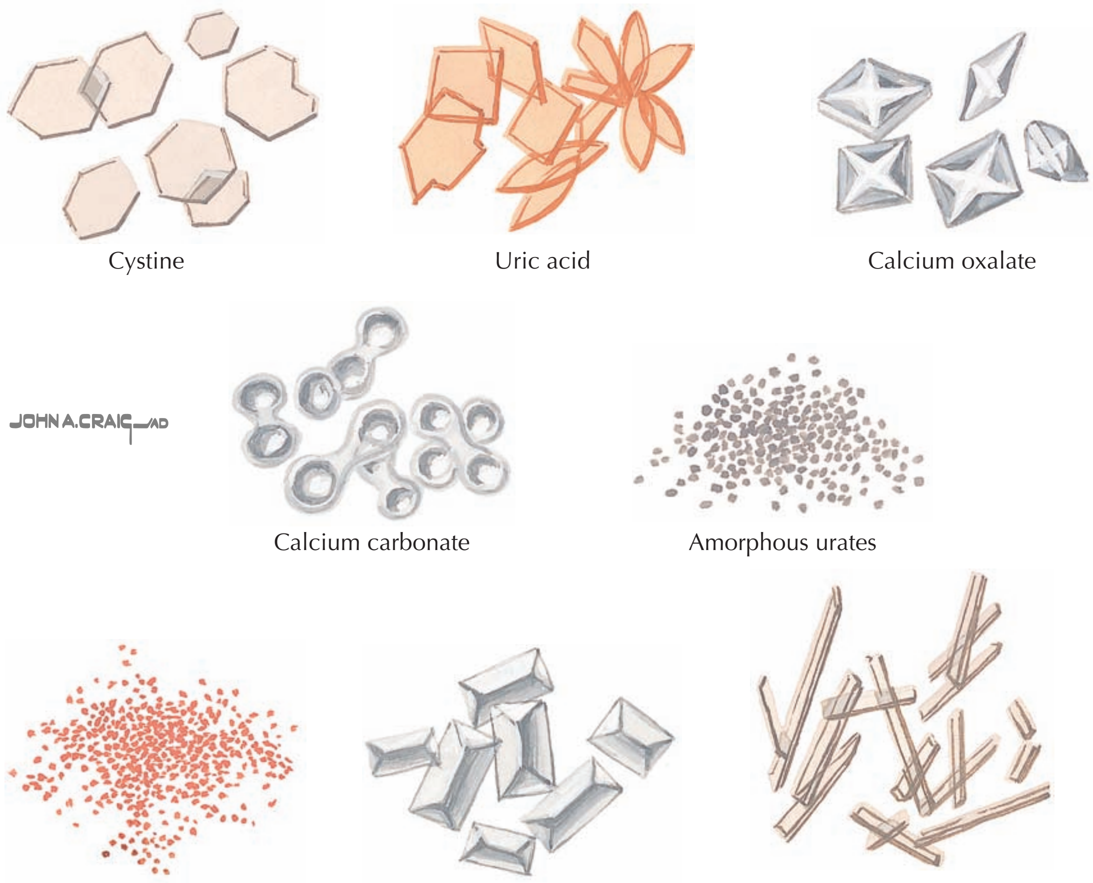
Formation of Renal Stones



Urine at equilibrium

Crystal formation

Morphology of urinary crystals



Cystine

Uric acid

Calcium oxalate

Calcium carbonate

Amorphous urates

Amorphous phosphates

Struvite

Calcium phosphate

Examination of urinary sediment for specific crystals may help identify specific types of urinary calculi

Renal stones are common, with lifetime prevalence estimates as high as 15%. Historically, men are affected more often than women, with a ratio of 2 or 3:1, although recent evidence suggests the gender gap may be closing. Stones can form at any age, but most occur in adults between 30 and 60 years of age. The clinical and economic impact of stone disease is substantial, with an estimated $2 billion spent in the United States in 2000.

Bladder stones are also associated with significant morbidity but occur far less frequently than renal stones. Because the causes of renal and bladder stones are distinct, their associated symptoms, treatments, and prevention strategies are considered separately.

RENAL STONES

Pathogenesis. The majority of renal stones (80%) are calcium-based, most frequently calcium oxalate and less commonly calcium phosphate. Other less common stone compositions are uric acid, struvite, and cystine.

When stone-forming salts reach a urinary concentration that exceeds the point of equilibrium between dissolved and crystalline components, crystallization will occur. Although certain chemicals in the urine can delay stone formation, there is a concentration of stone-forming salts above which crystallization becomes inevitable. Thus factors that increase the propensity for stone formation do so by reducing urine volume, increasing the quantity of stone-forming salts, or decreasing the quantity of crystallization inhibitors.

The process by which crystal formation leads to stone formation remains incompletely understood. Recent evidence, however, suggests that routine calcium oxalate stones originate on calcium phosphate deposits, known as Randall plaques, that are located at the tips of renal papillae and act as niduses for crystal overgrowth.

Risk Factors. Calcium stones are associated with a variety of genetic, environmental, and dietary risk factors. Elevated urinary calcium levels, one of the most common causes of calcium stones, can occur in the setting of increased bone resorption, intestinal hyperabsorption of calcium, or impaired renal tubular reabsorption of calcium. Elevated urinary oxalate levels, either dietary or the result of enhanced intestinal oxalate absorption, increase the urinary saturation of calcium oxalate and promote stone formation.

Depressed urinary citrate levels, often idiopathic but in some cases associated with systemic acidosis or hypokalemia, are also associated with an increased risk of calcium stones because citrate is an important inhibitor of stone formation. Finally, elevated urinary uric acid levels promote calcium oxalate stone formation and are associated with excessive intake of animal protein, conditions that lead to overproduction/overexcretion of uric acid (e.g., Lesch-Nyhan syndrome), or use of uricosuric medications.

Noncalcium stones are also associated with specific metabolic, genetic, and infectious disorders. Uric acid stones primarily occur in the setting of overly acidic urine, in which uric acid crystallizes. These stones are more common among patients with insulin resistance and type II diabetes mellitus, in whom production and excretion of ammonia in the renal proximal tubule is impaired, leading to insufficient buffering of protons in urine. Magnesium ammonium phosphate (struvite) stones, in contrast, occur in the setting of overly alkaline urine, in which struvite and calcium carbonate precipitate. These stones primarily occur in patients who have urinary tract infections with urea-splitting bacteria, such as *Proteus*, *Pseudomonas*, *Klebsiella*, and *Staphylococcus*. The hydrolysis of urea produces high concentrations of ammonia, which buffers protons. Incorporation of bacteria into these stones may cause chronic infections. Finally, cystine stones occur because of an inherited disorder of amino acid transport in

UROLITHIASIS *(Continued)*

which proximal tubular reabsorption of dibasic amino acids (cystine, lysine, ornithine, arginine) is impaired, leading to high urinary concentrations. Because cystine is poorly soluble in urine, it crystallizes and forms stones at relatively low urinary concentrations.

Presentation and Diagnosis. The symptoms associated with renal stones depend on their location. Typically, stones located within the calyces are asymptomatic. When these stones become detached and are propelled down the narrow ureter, however, they frequently become impacted. Stones generally become lodged in the narrowest portions of the ureter, which are located at the ureteropelvic junction, the crossing of the iliac vessels, and the ureterovesical junction (see Plate 6–4).

The first sign of a stone in the ureter is often the acute onset of severe flank pain. The stone obstructs urine outflow from the kidney, and the acute increase in renal pelvic pressure causes distention of the collecting system and stretching of the renal capsule, producing pain that classically starts in the flank and radiates to the ipsilateral groin. For reasons that are incompletely understood, the pain of a ureteral stone is typically intermittent, rather than constant. Other symptoms include nausea, vomiting, and gross or microscopic hematuria. This constellation of symptoms is known as renal colic. Occasionally, the movement of a stone into the ureter can be associated with obstruction and infection, culminating in pyelonephritis (see Plate 5–5) and/or sepsis. In this situation, urgent relief of obstruction is required to decompress the collecting system and allow antibiotics to be excreted into the urine.

Most renal stones can be detected on plain abdominal radiographs because of their calcium content, although calcium-poor stones such as pure uric acids stones are radiolucent. The primary diagnostic imaging tool, however, is non–contrast enhanced CT, which has a 98% sensitivity for the detection of stones. If intravenous contrast is administered and excreted into the urine collecting system, stones may be obscured, since both stones and contrast have high attenuation.

If a stone is identified, microscopic analysis of urine may be helpful to determine stone composition, as characteristic crystals are sometimes seen.

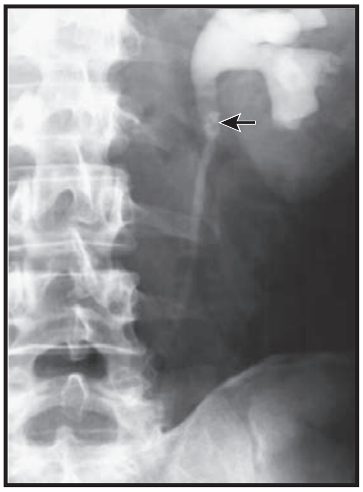
Treatment. The treatment of a renal stone depends on its size, location, and associated symptoms. The majority of stones that enter the ureter will pass on their own, given enough time. The likelihood of spontaneous stone passage is higher for stones that are small and/or located in the distal ureter. The time interval to stone passage is variable, and intermittent episodes of pain may accompany stone transit. Once they reach the bladder, most stones can easily be voided, as the lumen of the urethra is much larger than that of the ureter.

Medications such as calcium channel blockers and α-receptor antagonists have been shown to influence ureteral contractility and promote stone passage, thereby increasing the likelihood of spontaneous passage, reducing the time interval to passage, and decreasing the need for pain medication. A trial of these medications is indicated in patients with ureteral stones less than 1 cm in size, particularly if they are located in the lower part of the ureter at the time of diagnosis.

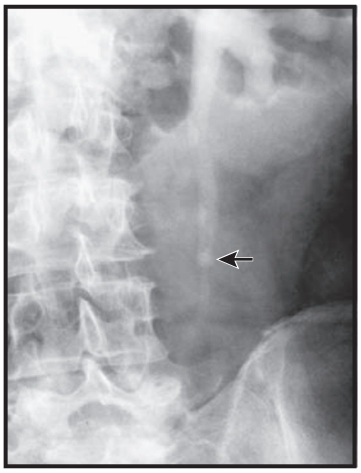
When a ureteral stone fails to pass or is too large to pass, or when pain becomes intolerable, surgical intervention is warranted. Many small to moderate-sized stones can be treated noninvasively, using shock waves focused on the stone under fluoroscopic or ultrasound guidance (extracorporeal shockwave lithotripsy, see Plate 10-12). Repeated application of focused shockwaves causes stone fragmentation, which enables painless passage of fragments in the urine. Alternatively, stones can be removed using a ureteroscope (see Plate 10-33), which is passed through the urethra and bladder up to the site of the stone in the ureter. The stone is then fragmented with a laser or other device inserted through the working channel of the ureteroscope.

For large and/or complex stones, such as staghorn calculi (which occupy all or a large portion of the collecting system), a large endoscope is introduced percutaneously into the kidney through a small incision in the flank. The stone is then fragmented and the

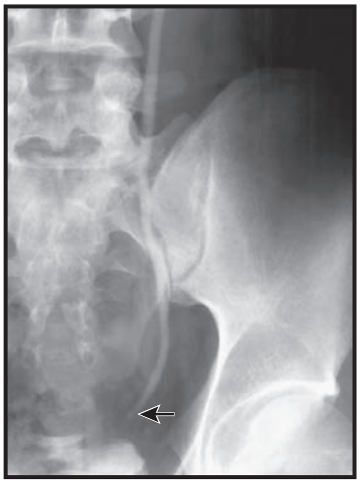
MAJOR SITES OF RENAL STONE IMPACTION



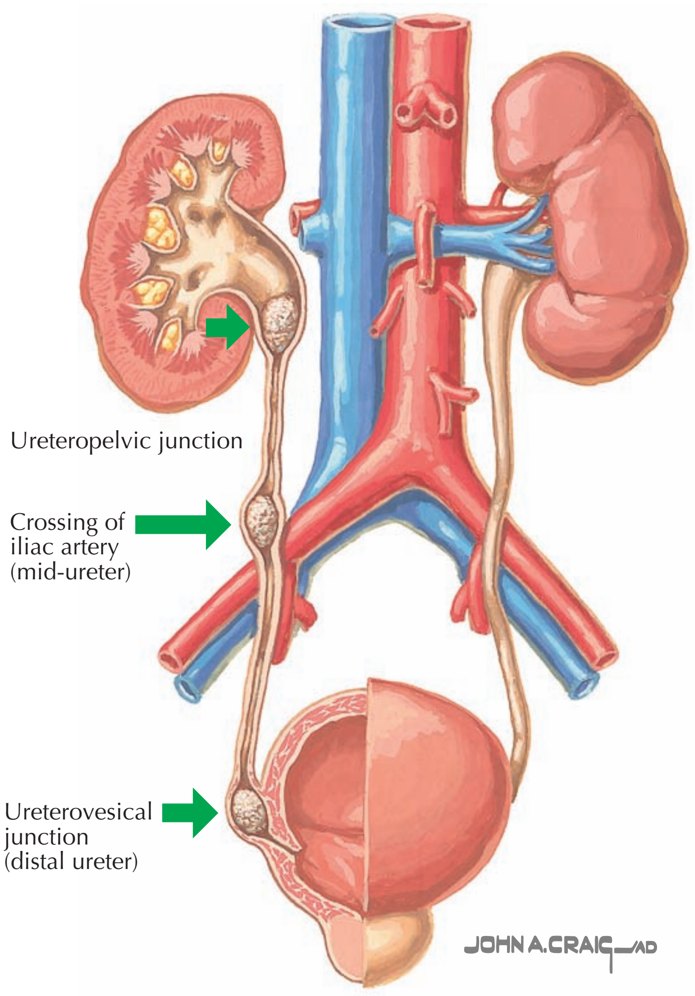
Stone at ureteropelvic junction

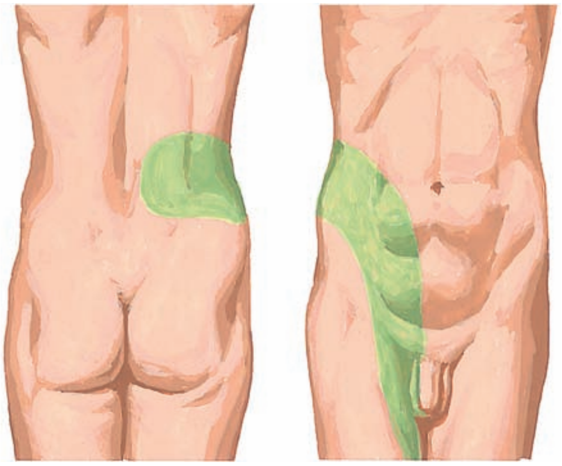


Stone in mid-ureter



Stone in distal ureter

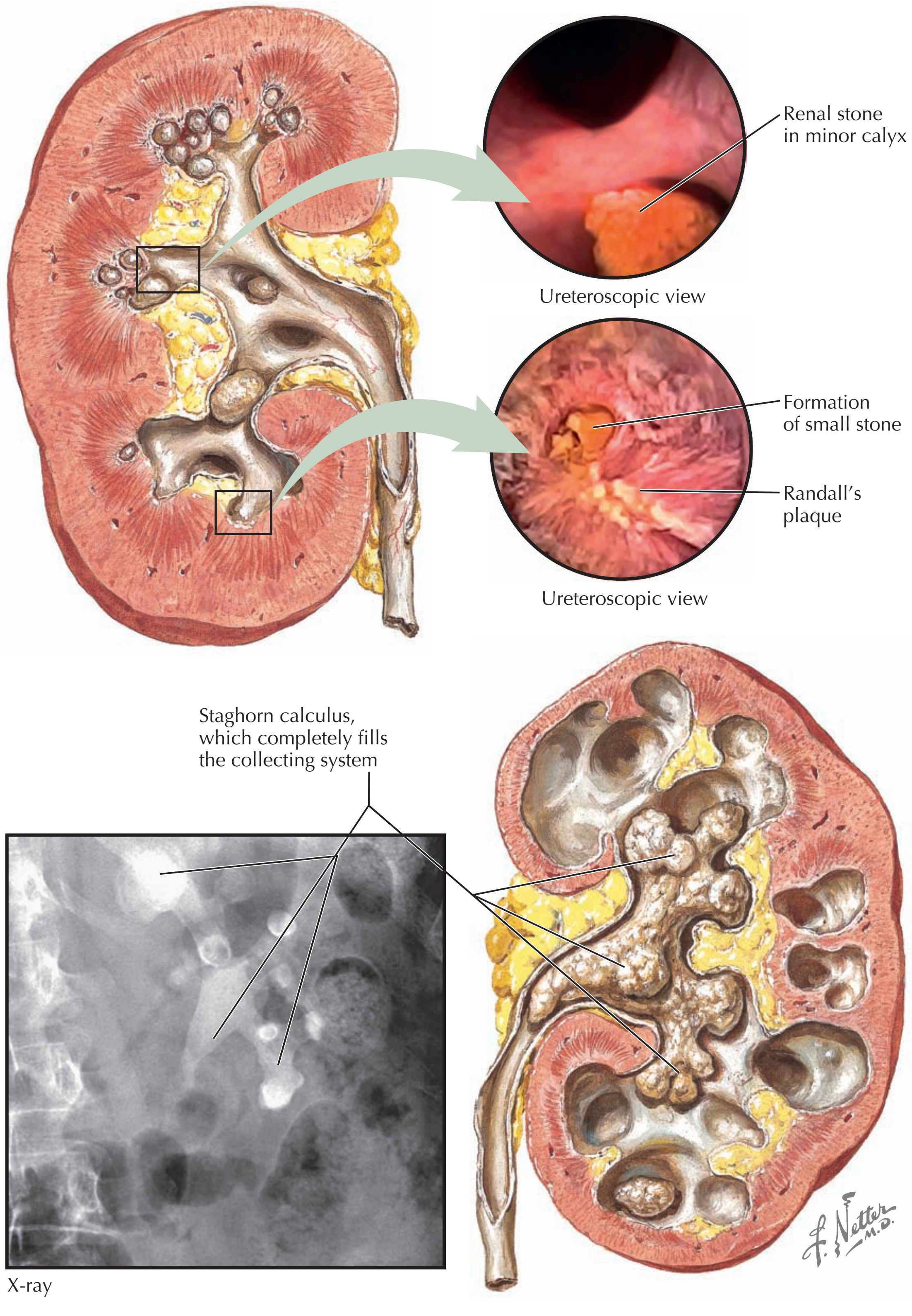

Ureteropelvic junction
Crossing of iliac artery (mid-ureter)
Ureterovesical junction (distal ureter)
JOHN A.CRAIG—AD



Distribution of pain in renal colic

UROLITHIASIS *(Continued)*

APPEARANCE OF RENAL STONES


Renal stone in minor calyx
Ureteroscopic view
Formation of small stone
Randall's plaque
Ureteroscopic view
Staghorn calculus, which completely fills the collecting system
X-ray

fragments removed (percutaneous nephrostolithotomy, see Plate 10-13).

Prognosis. After a first renal stone is diagnosed, there is a nearly 50% likelihood of recurrence over the next 5 to 10 years. With medical and dietary therapy, however, the recurrence rate can be significantly reduced.

Prevention strategies generally aim to correct underlying risk factors with diet or medication. Dietary changes that can lower the risk of calcium stones include an increase in fluid intake (sufficient to produce a urine volume of >2 L daily), limitation of salt intake (which reduces urinary calcium excretion), modest restriction of animal protein, and a reduction in consumption of oxalate-rich foods (such as nuts, chocolate, brewed tea, and dark green leafy vegetables). Severe dietary calcium restriction is discouraged in any stone former, but for patients with elevated urinary calcium levels, a modest reduction in calcium intake is recommended.

Medications can also help prevent stone formation. For patients with calcium stones, thiazide diuretics can help reduce urinary calcium excretion. For patients with uric acid stones, alkalizing agents such as potassium citrate can increase uric acid solubility. In the minority of patients with elevated urine uric acid levels, allopurinol may also be used.

Finally, underlying medical disorders that favor stone formation should also be treated, such as hypercalcemia associated with hyperparathyroidism.

BLADDER STONES

Primary bladder stones form within the bladder and are distinct from stones that originate in the kidney and pass into the bladder. Although bladder stones were common in the past, improvements in nutrition have substantially reduced their incidence, since dietary phosphate deficiency and excess ammonia excretion can contribute to stone formation. In developing countries, however, bladder stones remain common.

In industrialized nations, bladder stone formation is usually related to urinary stasis or urinary infection with urea-splitting bacteria (e.g., *Proteus mirabilis*). Indeed, these conditions often coexist, since urinary stasis predisposes to infection. Bladder stones are typically composed of calcium phosphate, uric acid, or struvite.

The most common disorder associated with incomplete bladder emptying and bladder stone formation is benign prostatic hyperplasia (BPH). In affected patients, treatment consists of transurethral prostate resection and laser or pneumatic stone fragmentation. In the case of a very large prostate, open prostatectomy and bladder stone removal may be necessary.

Another disorder associated with bladder stone formation is neurogenic bladder (see Plate 8-2), which occurs when neurologic disorders such as spinal cord injury, multiple sclerosis, or spina bifida interfere with normal voiding. Patients with neurogenic bladder who have long-term indwelling catheters are particularly prone to bladder calculi because of their increased rate of infection with urea-splitting organisms. The bladder stones are most commonly treated with endoscopic fragmentation and removal, with open surgery only rarely performed. The risk of further stone formation can be decreased with intermittent rather than indwelling catheterization, increased hydration, and bladder irrigation with weakly acidic solutions, such as acetic acid. Antibiotics are rarely indicated because bacteriuria is essentially unavoidable, and overuse of antibiotics may promote resistance.

The symptoms of bladder calculi are typically less obvious than those associated with kidney stones. Some patients may be completely unaware that they have a stone, while others may complain of urgency and frequency of urination, pelvic pain, or hematuria. These symptoms are also commonly associated with the underlying condition that leads to stone formation, such as bladder outlet obstruction or bladder infection.

URETEROPELVIC JUNCTION OBSTRUCTION

Obstruction of the ureteropelvic junction (UPJ), located where the renal pelvis meets the proximal ureter, typically reflects congenital abnormalities of either the ureter or surrounding structures. These are often detected during routine ultrasound examination of a growing fetus. The incidence of congenital UPJ obstruction is approximately 1:1000, with a slight male and left-sided predominance. In 10% to 40% of cases, the obstruction is bilateral.

PATHOGENESIS

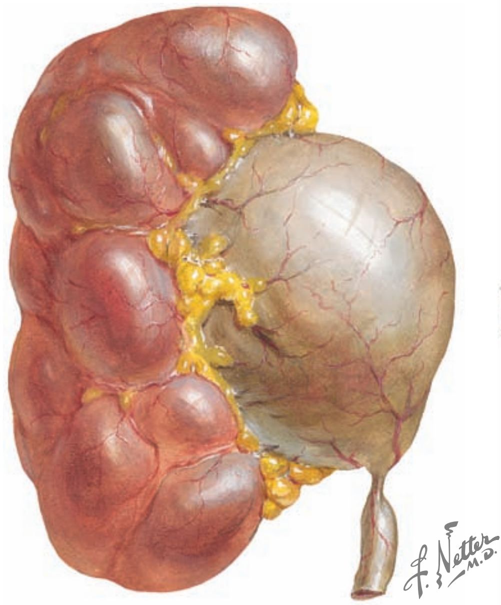
There are multiple possible causes of congenital UPJ obstruction, which include:

- A congenital lack of spiral muscle around the affected segment of the renal pelvis
- Developmental failure to recanalize the ureteral lumen
- Ureteral kinking that results from persistence of ureteral folds, which normally disappear during development
- Insertion of the ureter superior to the most dependent portion of the renal pelvis, thereby limiting drainage
- Direct compression by accessory vessels crossing from the renal artery or aorta to the lower pole of the kidney (i.e., extrinsic obstruction)

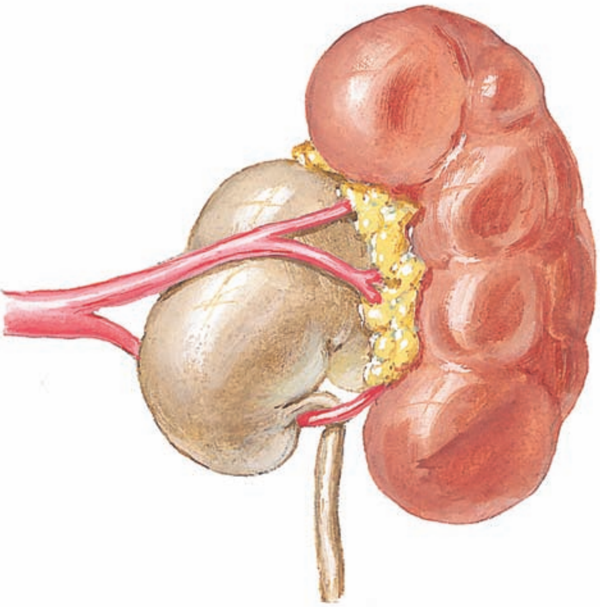
Acquired UPJ obstruction, in contrast, may occur during childhood or adulthood, typically in the setting of stones, chronic inflammation with stricture formation, polyps, malignancy, or surgical insult.

PRESENTATION AND DIAGNOSIS

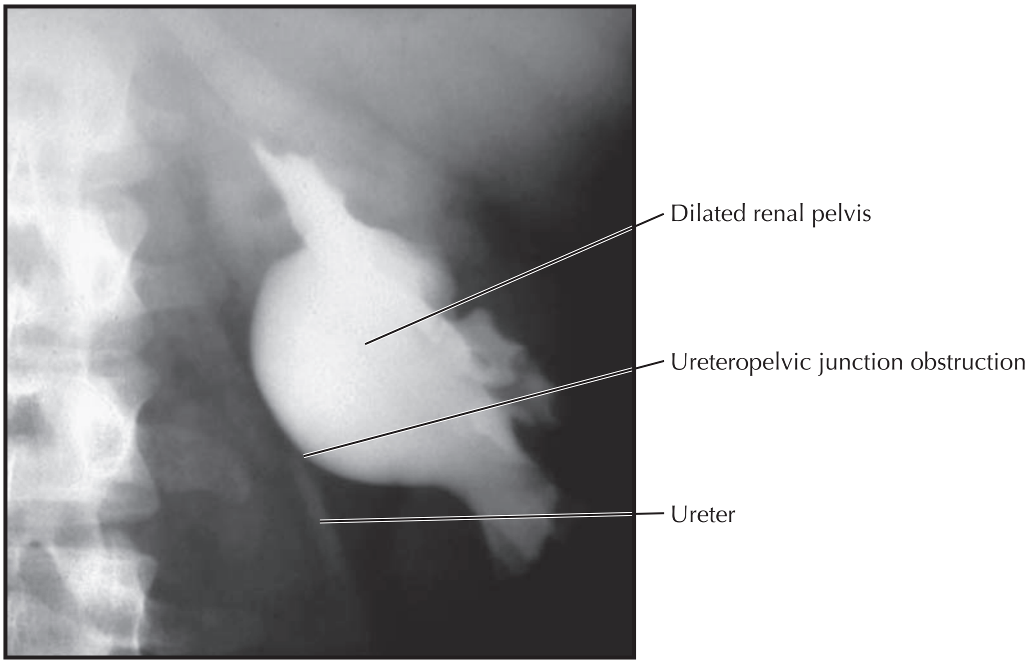
In fetuses and neonates, the diagnosis is usually first suspected when unilateral or bilateral intraparenchymal hydronephrosis accompanies normal ureteral width. In some circumstances, it may be difficult to distinguish the dilated calices seen in hydronephrosis from the large intraparenchymal cysts seen in multicystic dysplastic kidney (MCDK). Radiographic continuity between the dilated regions suggests hydronephrosis, while dilated regions that are distinctly separate favors MCDK. Nuclear scanning may help further differentiate the two conditions because radiotracer will concentrate in the hydronephrotic kidney, which retains some function, but not in the MCDK, which lacks function. In cases of bilateral hydronephrosis, high grade unilateral hydronephrosis, or congenital abnormalities such as horseshoe kidney, voiding cystourethrogram may be indicated to assess for vesicoureteral reflux (see Plate 2-21) and other causes of congenital hydronephrosis.



Intrinsic UPJ obstruction secondary to narrowing of the proximal ureteral lumen.



Extrinsic UPJ obstruction secondary to compression by an accessory lower pole renal artery.



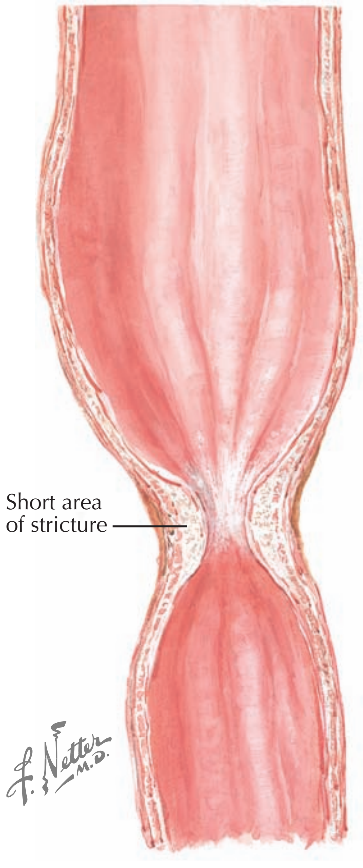
Intravenous pyelogram

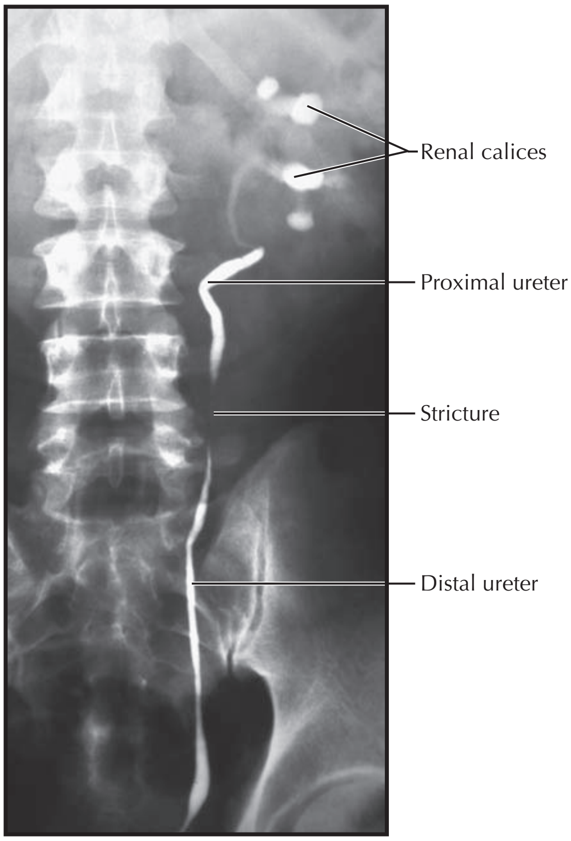
In older children and adults, undiagnosed congenital or acquired UPJ obstructions may cause intermittent, severe flank pain following increased fluid or diuretic intake. In addition, patients may experience hematuria after mild trauma, the theory being that distention of the renal pelvis causes mucosal vessels to become more friable. The diagnosis of UPJ obstruction in this population is often first suggested on contrast-enhanced CT or ultrasound. In adults and children older than 3 months of age, diuretic renography using 99mTc-MAG3 nuclear tracer should be performed once negative urine cultures have been obtained because it permits precise measurement of renal drainage. If a crossing vessel is suspected, duplex ultrasonography, CT angiography, or magnetic resonance angiography may help guide further management.

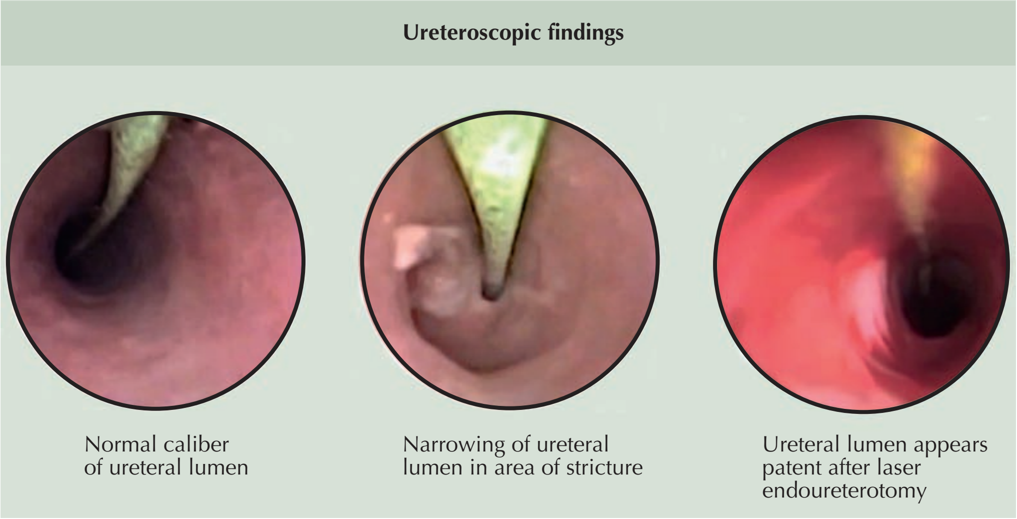
TREATMENT

Surgical intervention for UPJ obstruction is indicated for increased hydronephrosis on ultrasound (initially performed every 1 to 3 months), symptoms, stones, infection, deterioration of renal function, or hypertension. Techniques for intervention are primarily minimally invasive, and common ones are described in detail in Plate 10-16. A subset of neonates with suspected UPJ obstruction have spontaneous resolution, and efforts to prospectively identify these patients are ongoing.

URETERAL STRICTURES


Gross appearance


Retrograde pyeloureterogram


Ureteroscopic findings

Normal caliber of ureteral lumen

Narrowing of ureteral lumen in area of stricture

Ureteral lumen appears patent after laser endoureterotomy

Ureteral strictures cause narrowing of the ureteral lumen, and they can reflect either ischemic or nonischemic damage to the mucosa with subsequent fibrosis. Ischemic strictures are caused by a devascularization of the periadventitial blood supply, which may occur after surgical mobilization of the ureter, renal transplantation, or radiation therapy. Nonischemic strictures may be caused by ureteral instrumentation, infection (e.g., pyelonephritis, tuberculosis, schistosomiasis), inflammatory periureteral disease, or malignancy.

PRESENTATION AND DIAGNOSIS

Patients with acute ureteral obstructions of any kind typically have flank pain, which may be accompanied by nausea and vomiting. Chronic obstructions are often asymptomatic, although some may cause urosepsis or, if bilateral, renal insufficiency.

The gold-standard imaging study for evaluation of the ureter is contrast-enhanced CT. If any chronic ureteral obstruction is present, the more proximal segments will appear dilated. If a stricture is present, progressive narrowing of the ureter may be seen on delayed urographic phase, with little or no contrast seen in the distal segment if the narrowing is severe. If, in contrast, a stone is present, it will be visible as a discrete, hyperattenuating region in the ureter. If a ureteral mass is present, a filling defect may be seen.

Once a stricture has been diagnosed, a renal scan can be performed to quantify the function of each kidney. Such measurements are especially important if endoscopic treatment is being considered because the ipsilateral kidney should have at least 25% of normal filtration function for the intervention to have a high probability of success.

TREATMENT

Once a ureteral stricture has been diagnosed, the possible ongoing presence of secondary causes (especially malignancy) should be ruled out. The stricture should then be treated to relieve the pain of obstruction and prevent upper tract infection.

Endoscopic techniques, which are associated with less morbidity and faster recovery times than open procedures, should be employed for strictures that are 1 cm or less in length, located away from the midureter, present for less than 6 months, nonischemic in etiology, and associated with at least 25% remaining function in the ipsilateral kidney. Strictures that do not possess these characteristics should be treated using an open or laparoscopic surgical approach.

Endoscopic Treatment. A ureteral stent can be deployed as a temporizing measure in patients with pain or urosepsis. In the occasional patient with significant comorbidities who is a poor candidate for more invasive procedures, a stent may be used as definitive management, although it should be changed every 3 to 12 months. Occasionally, if a very tight obstruction is seen, two side-by-side stents may be necessary to provide adequate drainage.

Balloon dilation may be performed to recanalize the strictured segment, but recurrent stricture formation is common. Retrograde pyeloureterography is first performed to delineate ureteral anatomy and the precise location of the stricture. Next, a balloon catheter is placed under fluoroscopic guidance so that it traverses the strictured segment. If placement is challenging, a ureteroscope can be used to directly visualize the process (see Plate 10-33). Once appropriately positioned, the balloon is briefly inflated, which stretches and dilates the strictured segment.

An endoureterotomy consists of stricture incision under direct vision through a ureteroscope. Several different technologies can be employed, including cold knife incision, electrocautery, and holmium laser ablation. All require a full-thickness cut through the wall of the ureter into the periureteral fat. The optimal direction of the incision depends on the level of the ureter that is affected. Incisions into the pelvic ureter should be made in an anteromedial direction, so as to avoid the iliac vessels. Meanwhile, incisions into the upper ureter should be made in a posterolateral direction, so as to avoid the aorta and inferior vena cava.

Surgical Treatment. Open or laparoscopic excision of a ureteral stricture should begin with careful ureteral mobilization to minimize the risk of damage to the periureteral blood supply. Debridement of the scarred and fibrotic area should then proceed until a bleeding edge is reached. Finally, the ureter should be reconstructed in a manner that is tension-free, spatulated, and water-tight. A ureteral stent should be placed to ensure adequate postoperative drainage. The optimal method of reconstruction depends on the location and length of the excised segment. Several different options are available, as described in Plate 10-36.

SECTION 7

TRAUMATIC INJURIES

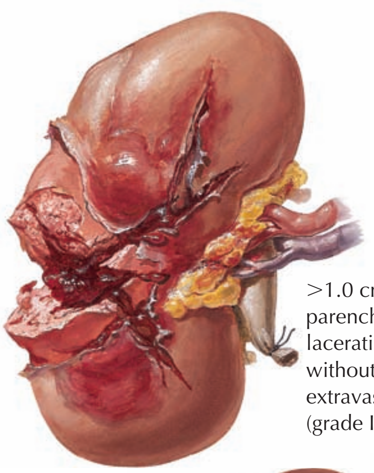
GRADING SYSTEM AND RENAL PARENCHYMAL INJURIES

Kidney Injury Scale (American Association for the Surgery of Trauma)

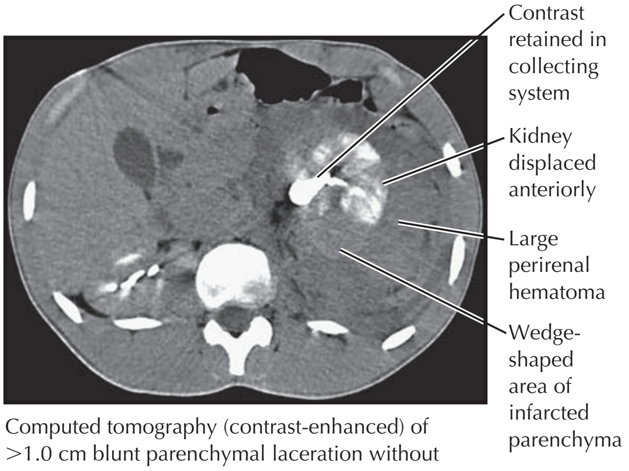
Grade*	Type of injury	Description of injury
I	Contusion	Microscopic or gross hematuria, urologic studies normal
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding perirenal hematoma confined to renal retroperitoneum
	Laceration	<1.0 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1.0 cm parenchymal depth of renal cortex without urinary extravasation
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla, and collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum, which devascularizes kidney

*Advance one grade for bilateral injuries up to grade III

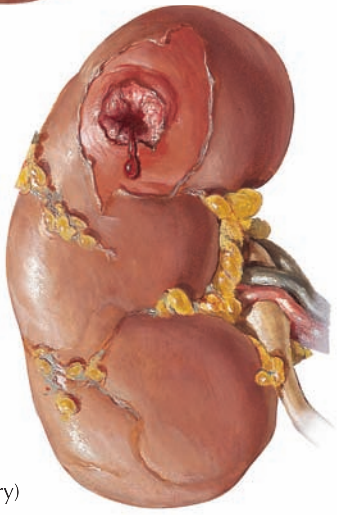
From Moore EE et al. Organ injury scaling: spleen, liver and kidney. J Trauma. 1989; 29(12): P1664-6.



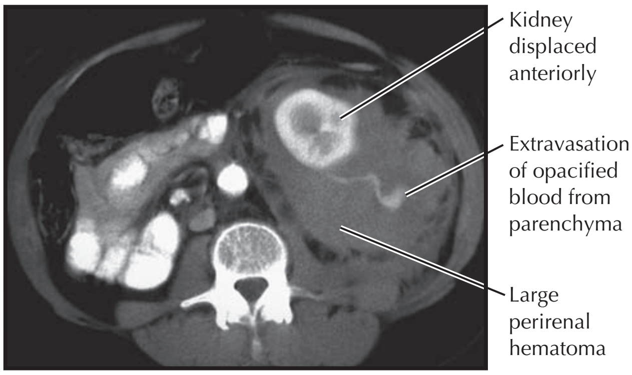
>1.0 cm blunt parenchymal laceration without urine extravasation (grade III injury)


Contrast retained in collecting system
Kidney displaced anteriorly
Large perirenal hematoma
Wedge-shaped area of infarcted parenchyma

Computed tomography (contrast-enhanced) of >1.0 cm blunt parenchymal laceration without urine extravasation (grade III)



>1.0 cm penetrating parenchymal laceration without urine extravasation (grade III injury)


Kidney displaced anteriorly
Extravasation of opacified blood from parenchyma
Large perirenal hematoma

Computed tomography (contrast-enhanced) of >1.0 cm penetrating parenchymal laceration without urine extravasation (grade III)

RENAL INJURIES

The kidney is injured in up to 5% to 10% of all severe trauma cases. At most urban trauma centers, approximately 80% to 90% of kidney injuries are blunt, while the remainder are penetrating. Children are more likely to sustain blunt renal injuries because of the relative large size of their kidneys, scant perirenal fat, and incomplete rib ossification. Blunt renal injuries are often minor and heal spontaneously, whereas penetrating renal injuries are typically significant and often require intervention.

PRESENTATION AND DIAGNOSIS

Patients should be suspected of having renal injury if there is trauma to the flank, abdomen, or lower chest; flank ecchymosis or tenderness; low posterior rib fractures; or lumbar transverse process fractures. Although hematuria is the major symptom and is seen in the vast majority of cases, it may be absent in injuries to the renal pedicle or ureteropelvic junction. In addition, the degree of hematuria often does not correspond to the severity of the renal injury.

A detailed history must be obtained regarding the circumstances of the trauma. Falls or high-speed motor vehicle accidents, for example, may cause deceleration injuries to the renal pedicle. In the setting of gunshot wounds, it is important to determine if the injury is due to a high or low velocity missile because high velocity missiles often cause more extensive kidney injury and delayed necrosis.

The location of any abdominal penetration must also be carefully documented. For example, stab wound entrance sites posterior to the anterior axillary line and below the nipple line are unlikely to have associated intraperitoneal organ injury or to warrant abdominal exploration. The entrance and exit wound sites of a gunshot should be marked with radiopaque markers so that the missile path can be inferred on imaging.

In unstable patients who require immediate abdominal exploration, urologists often advocate for a one-shot intravenous pyelogram. Intravenous contrast is administered at 2 cc/kg of body weight, followed by a single abdominal radiograph 10 minutes later. The primary aim of this study is to determine the function of the contralateral kidney to avoid removing a solitary kidney. In many cases, however, it can produce ambiguous results that are difficult to interpret. Therefore, many trauma surgeons instead simply palpate the contralateral side to assess for the presence of a second kidney. Another option is to infuse intravenous methylene blue and temporarily occlude the ureter ipsilateral to the injured kidney. Blue urine in the Foley bag indicates a functional contralateral kidney.

In stable patients, indications for imaging a suspected kidney injury include:

1. Blunt trauma and gross hematuria
2. Blunt trauma, microscopic hematuria (>5 RBC/hpf), and shock
3. Major acceleration-deceleration injury
4. Penetrating flank, back, or abdominal trauma associated with gross or microscopic hematuria, or with a missile path that is in line with the kidney
5. Pediatric trauma with any degree of hematuria
6. Associated injuries/physical signs suggestive of underlying renal injury

In stable patients, computed tomography (CT) with intravenous contrast is the imaging study of choice for demonstrating renal parenchymal injury, perirenal/retroperitoneal hematomas, urine extravasation, injuries to the renal hilum, and associated intraabdominal organ injuries. It is essential to obtain both an arteriographic phase to assess for major vessel injury and a delayed pyelographic phase to assess for contrast extravasation.

Parenchymal contusions are noted as areas of reduced enhancement, whereas lacerations appear as linear, blood-containing areas that interrupt the parenchyma. Hematomas are visible as hyperattenuating collections that, if large and confined to the subcapsular space, can compress the adjacent renal parenchyma.

Ultrasonography is sometimes used as an initial screen but offers limited value. For example, although ultrasound can demonstrate perirenal fluid collections, it cannot distinguish fresh blood from extravasated urine.

RENAL INJURIES *(Continued)*

Arteriography and superselective embolization have important roles in the evaluation and treatment of posttraumatic delayed renal bleeding or pseudoaneurysms. In select cases, arteriography and endoluminal stent placement have also been successfully used to manage renal artery intimal tears and thrombosis from blunt trauma.

Based on the findings from imaging studies, injuries can be graded according to criteria set by the American Association for the Surgery of Trauma. The odds of intervention and nephrectomy rise with each increase in grade.

TREATMENT

Blunt renal injuries are often low-grade and can thus receive conservative management. Even if there is urine extravasation, spontaneous resolution is likely unless there is complete disruption of the UPJ (grade 5). Conservative management includes strict bed rest until hematuria resolves, frequent assessments of hematocrit, and reimaging after 3 to 5 days if there is urine extravasation. Persistent bleeding demands repeat imaging, arteriography, or surgical exploration. Worsening or symptomatic urine leaks often require ureteral stenting.

Penetrating renal injuries generally require exploration because they are often high grade and associated with other major organ damage. Roughly three fourths of renal gunshot wounds and half of renal stab wounds demand exploration.

The absolute indication for surgical exploration of any renal injury is persistent and potentially life-threatening bleeding. Such bleeding will occur if there is avulsion of the main renal artery or vein, or if there is "shattering" of the kidney by multiple deep lacerations. A pulsatile, expanding or unconfined retroperitoneal hematoma suggests ongoing bleeding that requires intervention.

Relative indications for surgical exploration include:

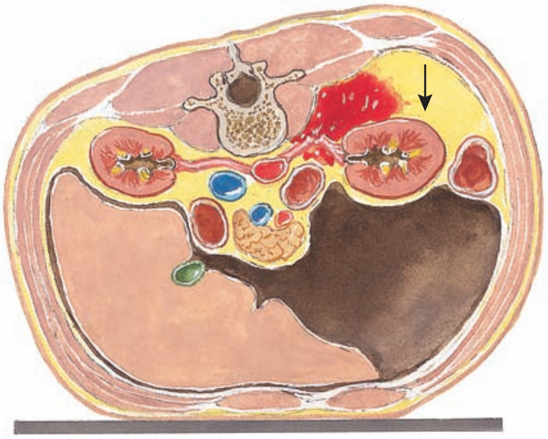
1. UPJ avulsion
2. High-grade penetrating renal injuries
3. High-grade blunt renal injuries where abdominal exploration is performed for other intraabdominal injuries
4. Devitalized renal parenchyma exceeds 50% of total
5. Persistent urinary leakage with failed endoscopic management
6. Persistent vascular injury with failed angiographic management
7. Bilateral renal artery thrombosis (or thrombosis in a solitary kidney)
8. Incomplete staging that demands either further imaging or renal exploration

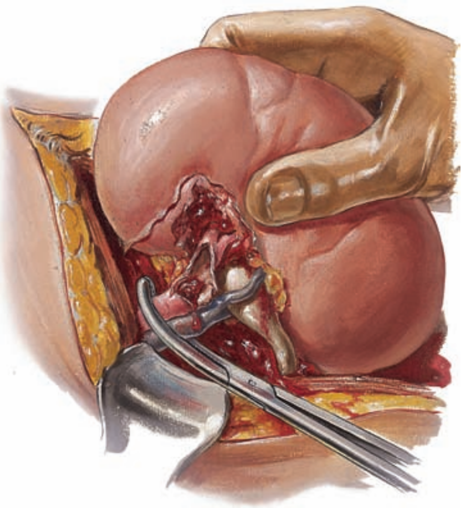
The injured kidney is best exposed through a midline transperitoneal incision. Proximal vascular control must be established before entering the renal fascia. If it is not, there is a high risk of releasing a tamponade and causing a massive bleed that necessitates a nephrectomy. When consistent proximal vascular control of the renal pedicle is performed, however, the nephrectomy rate for renal trauma is low.

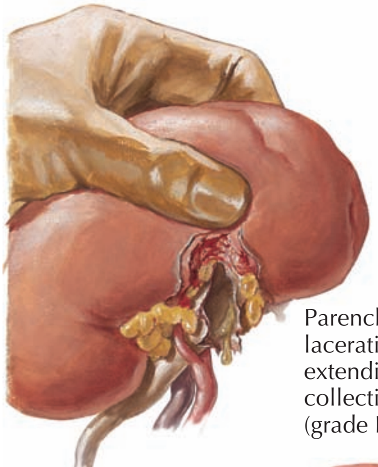
Repair of the damaged kidney requires broad exposure of the injured area, sharp excision of all nonviable parenchyma, meticulous hemostasis, watertight closure of the collecting system, and parenchymal defect closure over a bolster.

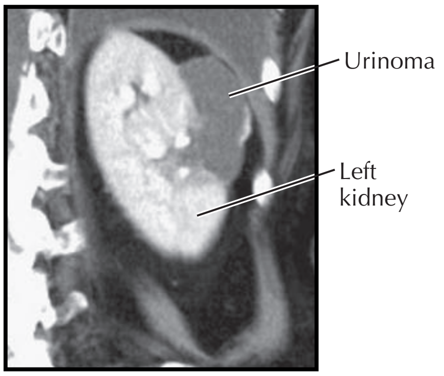
The most common complications after renal trauma include prolonged urinary extravasation, delayed bleeding, arterial pseudoaneurysm, abscess, urinary fistula, and hydronephrosis. Renovascular hypertension may occur after renal trauma but is almost always transient. A rare, sustained hypertension is usually seen with subcapsular hematomas that exert significant parenchymal compression, causing decreased renal perfusion and subsequent release of renin (a phenomenon known as Page kidney).

RENAL HILAR INJURIES


Acceleration-deceleration injury of renal hilar vessels (grade V injury) resulting from continued downward momentum of the kidney after sudden deceleration of the body on impact

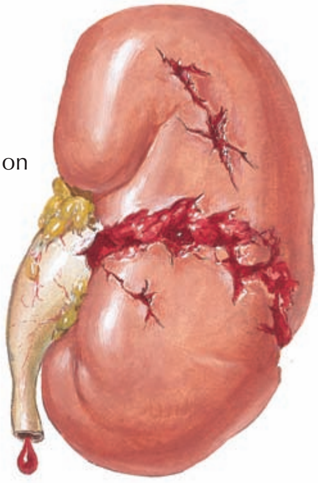

Injury to renal hilar vessels (grade V injury)

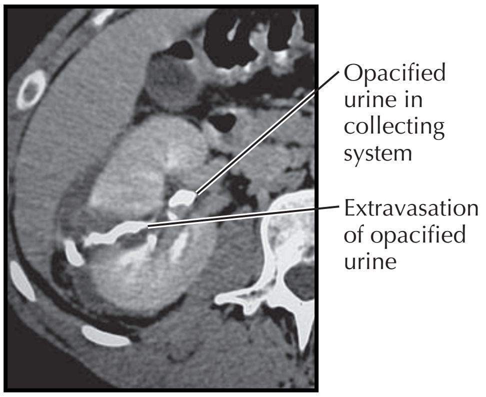

Parenchymal laceration extending through collecting system (grade IV injury)



Computed tomography (contrast-enhanced, coronal reconstruction) of laceration of collecting system (grade IV injury)

Parenchymal laceration extending through medulla and collecting system (grade IV injury)




Opacified urine in collecting system
Extravasation of opacified urine
Computed tomography (contrast-enhanced) of parenchymal laceration extending through collecting system (grade IV injury)

URETERAL INJURIES

The vast majority of ureteral injuries are iatrogenic, occurring during either open pelvic surgery or ureteroscopy. Injuries associated with open surgeries often affect the distal one third of the ureter and go undiagnosed until the postoperative period. The procedures most often implicated are transabdominal hysterectomy and abdominoperineal resection. Fortunately, such complications are rare, with the ureter injured in only 0.5% to 1.0% of all pelvic operations. Injuries incurred during ureteroscopy typically occur during the basketing and attempted removal of ureteral stones.

Ureteral injuries from external trauma are very rare, and more than 95% are related to penetrating wounds. Gunshot wounds account for the vast majority of such injuries; these can either directly rupture the ureter or cause severe contusions secondary to energy from the blast. Blunt injuries account for the remaining 5% of cases and can affect the ureter through several mechanisms. First, a deceleration injury may dislocate the kidney and cause tears at the fixation point of the ureteropelvic junction. In addition, hyperextension injuries of the back may cause avulsion of the ureter as it is stretched against the lower thoracic and lumbar vertebral bodies. This type of injury classically occurs in children struck by motor vehicles.

Successful surgical management of ureteral injuries requires a high index of suspicion, early diagnosis, and an intimate knowledge of ureteral anatomy and blood supply. If recognized and repaired promptly, a ureteral injury is usually associated with low morbidity. Delayed recognition of ureteral injuries, however, is common and results in significant morbidity, which can include a urinoma, stricture (with subsequent hydronephrosis), fistula, abscess, or sepsis.

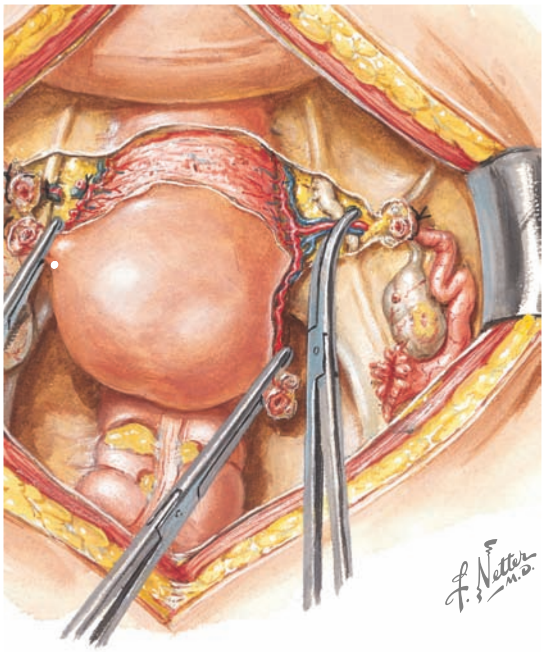
PRESENTATION AND DIAGNOSIS

Patients may complain of flank pain or hematuria, although the latter is not a reliable sign and is absent in up to 45% of penetrating and 67% of blunt ureteral injuries. Findings on physical examination may include costovertebral angle tenderness, flank ecchymosis, and an abdominal mass. In most cases, however, symptoms are nonspecific. Therefore, clinicians should focus on the patient history and maintain a low threshold for imaging.

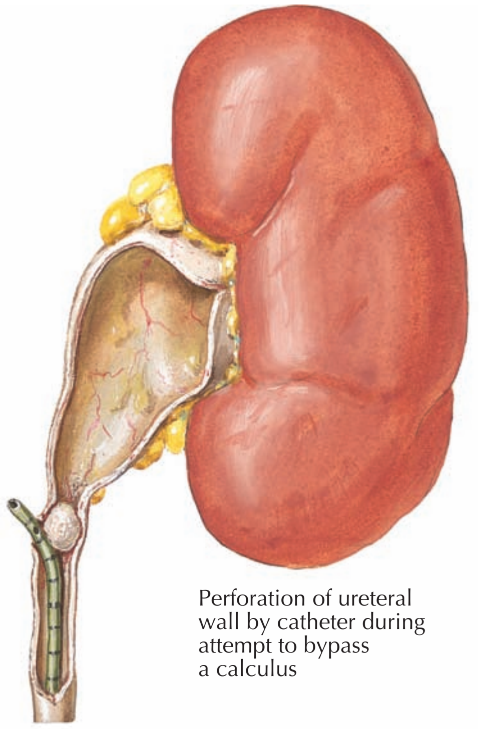
If intraoperative or blunt injury is suspected, CT with intravenous contrast and fine cuts through the ureter should be performed to determine the presence and location of contrast extravasation. Scans must be delayed long enough to visualize excretion of contrast in the ureter, which usually takes at least 10 minutes.

Although retrograde pyelography (RPG) is also sensitive enough to reveal most injuries, it is both time-consuming and cumbersome. Thus RPG has little role in the acute trauma setting and is reserved for the stable patient with an equivocal CT scan. If RPG is performed, however, it may be possible to treat the ureteral injury at the same time by deploying a stent.

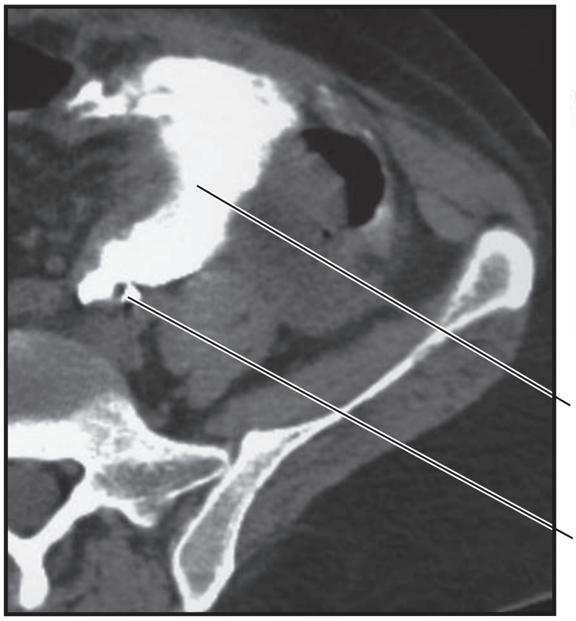
If there is a penetrating injury to the peritoneum, surgical exploration is required. The ureters should be examined for damage using intravenous or retrograde injection of indigo carmine, which will extravasate at injury sites.



Distal ureteral crush injury because of clamp intended for uterine vessels



Perforation of ureteral wall by catheter during attempt to bypass a calculus


Extravasation of opacified urine into intraperitoneal space
Ureter opacified by retrograde injection of contrast

Computed tomography of a surgical laceration of the ureter

TREATMENT

In patients who are too unstable to undergo ureteral reconstruction, a "damage control" approach is appropriate. Two common strategies include bringing the ureter to the abdominal wall (temporary cutaneous ureterostomy) or ureteral ligation followed by percutaneous nephrostomy. Definitive reconstruction is delayed until the patient stabilizes.

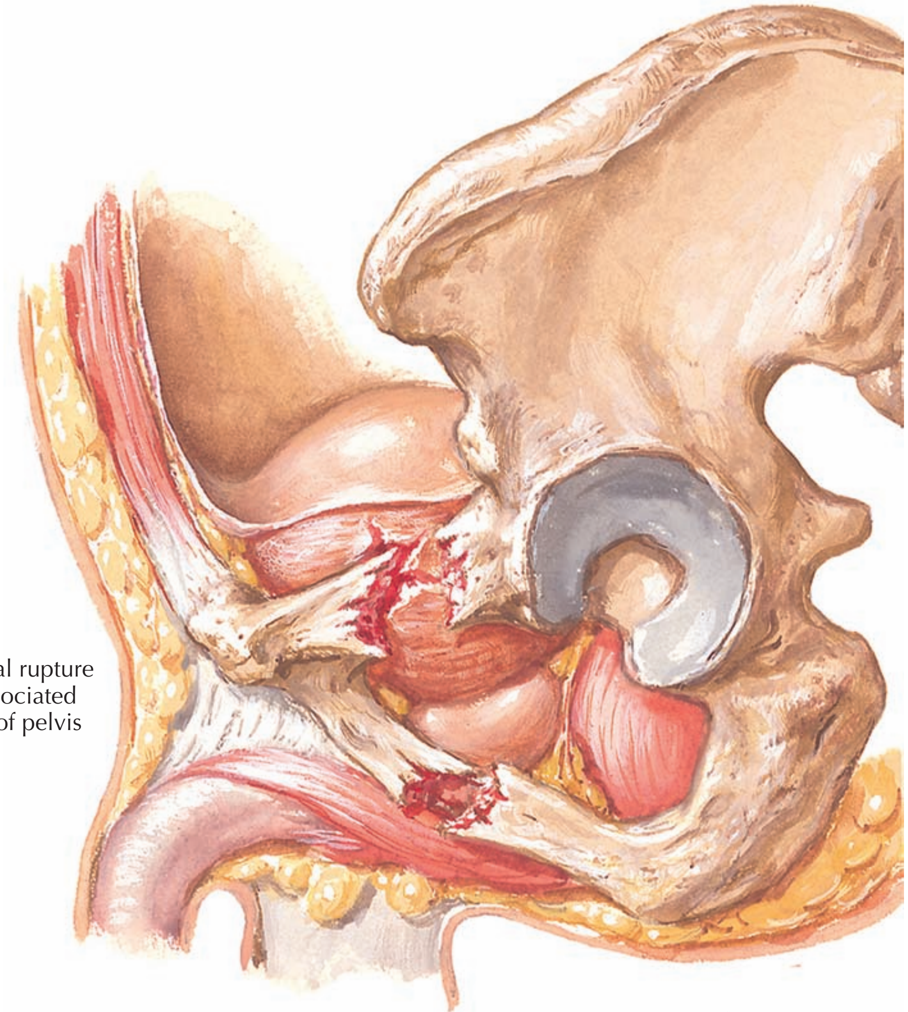
In stable patients, injuries should be explored and repaired.

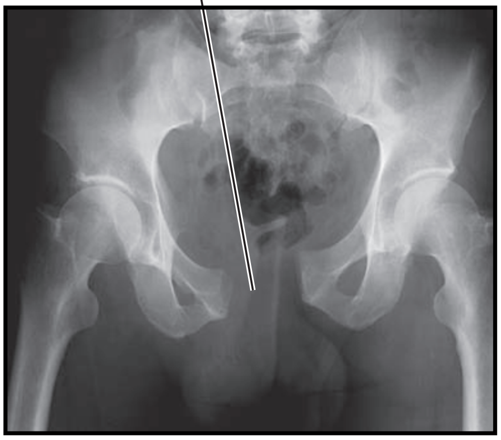
Ureteral contusions can lead to strictures if untreated and should thus be stented and drained. If the contusion is severe, the ureter should be segmentally resected; debrided until a bleeding edge is reached; reanastomosed tension-free over a stent; and drained.

Ruptures of the upper and midureter can be repaired with primary ureteroureterostomy, an end-to-end anastomosis over a stent. Ruptures of the distal ureter are repaired by reimplanting the ureter into the bladder (ureteroneocystostomy). If there is extensive loss of the distal ureter, a section of the bladder is sewn to the ipsilateral psoas minor tendon (psoas hitch) to help bridge the gap. The ureter is then reimplanted into the bladder. If the bladder is too small or noncompliant for stretching, a transureteroureterostomy can be performed, in which the injured ureter is brought across the midline and sewn to the side of the contralateral ureter. This procedure is also useful when there are associated rectal, pelvic, or vascular injuries.

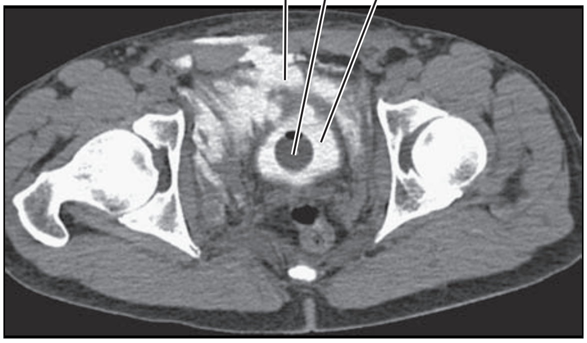
Complex reconstructions of extensive ureteral injuries may be performed on an elective basis but are not appropriate for acute management (see Plate 10-36). Such procedures include ileal interposition, in which the small bowel is used as a ureteral replacement; Boari flap, in which a section of the bladder is reconstructed as a tube; and autotransplantation, in which the kidney is relocated to the ipsilateral pelvis.

EXTRAPERITONEAL BLADDER RUPTURES





X-ray demonstrating pelvic fracture



Computed tomography of bladder demonstrates extraperitoneal rupture

BLADDER INJURIES

The vast majority of bladder injuries result from external trauma. Most cases result from blunt trauma, such as motor vehicle accidents, whereas a smaller number result from penetrating trauma, such as gunshot or stab wounds. A minority of bladder injuries not associated with external trauma are iatrogenic. The highest risk procedures include transabdominal hysterectomy, Cesarean section, transurethral resection of a bladder tumor, and bladder biopsy.

Bladder trauma may lead to contusions (partial-thickness mucosal tears resulting from blunt forces), interstitial injuries (partial-thickness lacerations that involve the serosa), and ruptures. The remainder of this section will focus on ruptures, which can be classified as either extraperitoneal or intraperitoneal based on the region of the bladder wall that tears, which determines the consequent site of urine collection. Overall, approximately 60% of ruptures are extraperitoneal, 30% are intraperitoneal, and 10% are combined.

Extraperitoneal ruptures involve the lateral or inferior surfaces of the bladder, which are not in contact with peritoneum. Urine extravasates into the pelvis and collects around the base of the bladder. This type of rupture almost always occurs in the setting of a pelvic fracture, resulting from the shearing forces of the pelvic fragments, rather than from perforation by bony spicules. If additional fascial planes are disrupted, urine may extend into the abdominal wall, thigh, and genitals.

Intraperitoneal ruptures, in contrast, involve the superior surface (dome) of the bladder, which is covered with peritoneum. As a result, urine extravasates into the intraperitoneal space. This type of rupture occurs when a full bladder is subject to a sudden and dramatic increase in pressure. The bladder's superior surface has the most widely spaced muscle fibers and is thus most likely to rupture. A common victim is a person with a full bladder who is wearing a seatbelt during a motor vehicle accident.

PRESENTATION AND DIAGNOSIS

Hematuria is a nearly universal feature of bladder rupture. Other signs include suprapubic tenderness, lower abdominal bruising, and low urine output. On laboratory assessment, patients may be found to have elevated serum creatinine concentration, acidosis, hyperkalemia, and azotemia secondary to reabsorption of extravasated urine. Women should receive a careful pelvic examination to assess for possible vaginal injuries, which can result in vesicovaginal fistulae. In addition, patients should be assessed for urethral injuries, which can lead to difficulty with voiding.

After blunt trauma, an absolute indication for imaging the bladder is the combination of pelvic fracture and gross hematuria. Relative indications include gross hematuria without pelvic fracture, as well as microhematuria with or without pelvic fracture, occurring with any of the following: the clinical signs and symptoms listed previously, free intraperitoneal fluid on abdominal imaging, or known prior bladder abnormality.

BLADDER INJURIES *(Continued)*

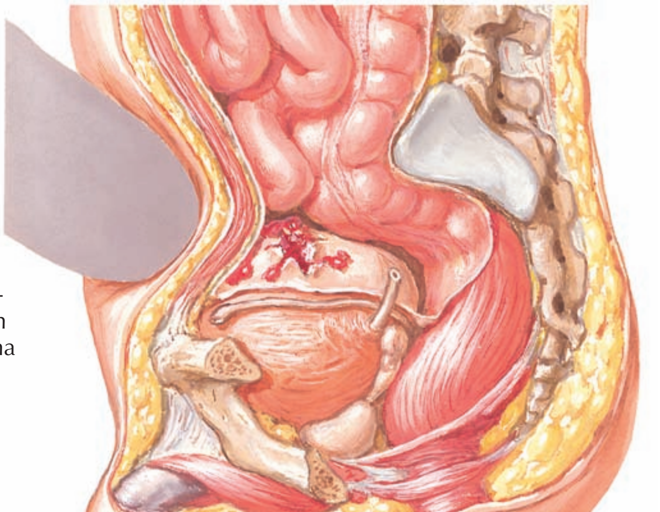
After penetrating trauma of the pelvis, lower abdomen, or buttocks, imaging of the bladder is mandatory if there is any degree of hematuria.

In most patients, computed tomographic cystography is the initial imaging test of choice. After urethral injury has been excluded, a Foley catheter is placed and the bladder is retrograde filled with 350 to 400 mL of dilute contrast. This imaging modality is highly sensitive for the detection of tears and also permits evaluation of other abdominopelvic organs. The previous gold standard was conventional cystography; however, this test often requires more time and may fail to detect subtle tears. In addition, post drainage films must be obtained. Of note, neither ultrasound nor CT scan without bladder contrast is sensitive enough to be an effective screening tool.

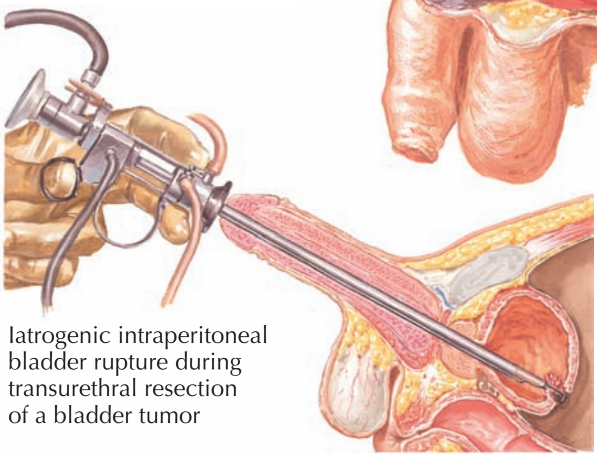
Using the appropriate imaging techniques, bladder ruptures may be characterized based on the location and extent of contrast extravasation. As previously noted, extraperitoneal ruptures lead to contrast extravasation into the pelvis. Meanwhile intraperitoneal ruptures cause contrast extravasation around loops of the bowel and into the paracolic gutters. Injuries less severe than a complete rupture may also be detected. Interstitial injuries cause contrast accumulation within the bladder wall with minimal extravasation. Contusions often do not cause any radiographic abnormalities but may, in some cases, result in an abnormal bladder contour.

If an iatrogenic bladder injury is suspected during a surgical procedure, a Foley catheter should be placed, and the bladder should be filled with either methylene blue (in open cases) or contrast (in endoscopic cases) to determine if there is extravasation into the abdomen.

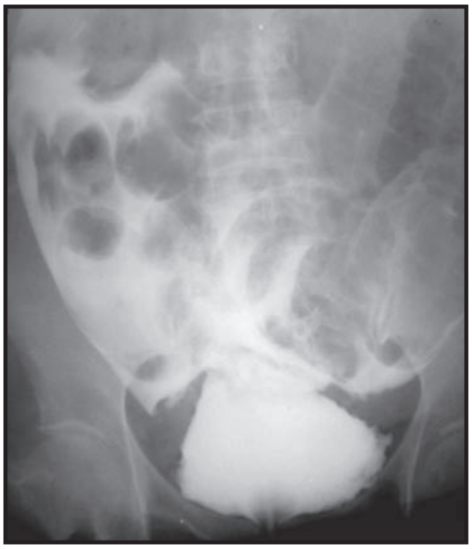
INTRAPERITONEAL BLADDER RUPTURES



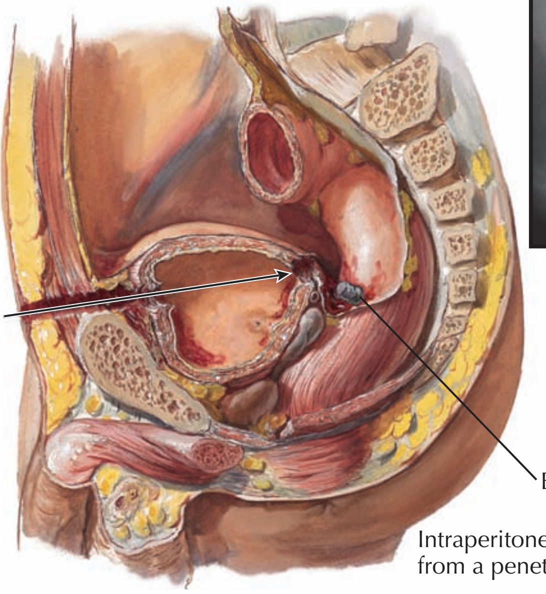
Intraperitoneal rupture of distended bladder resulting from blunt lower abdominal trauma (most common mechanism)



Iatrogenic intraperitoneal bladder rupture during transurethral resection of a bladder tumor



Retrograde cystogram of an intraperitoneal bladder rupture. Contrast extravasates into the intraperitoneal space and surrounds loops of bowel.



Intraperitoneal bladder rupture resulting from a penetrating gunshot wound

TREATMENT

Most blunt extraperitoneal bladder ruptures can be successfully managed with catheter drainage alone and do not need to be explored. In most cases, the bladder will heal spontaneously over the course of several weeks, which can be confirmed with a follow-up cystogram. If the abdomen is explored because of other injuries, however, extraperitoneal ruptures can be repaired at the same time.

In contrast, blunt intraperitoneal ruptures require open repair. Delayed management often results in significant morbidity, including metabolic acidosis, ileus, abdominal/pelvic pain, sepsis, and possibly peritonitis.

Penetrating bladder injuries mandate surgical exploration to assess for other intraabdominal injuries and to determine if there is damage to the ureters or trigone.

To explore injuries, the bladder should be exposed through a midline abdominal incision and opened at the dome. This precaution minimizes the risk of incising a pelvic hematoma, which can cause brisk, difficult-to-control bleeding. All tears should be repaired from within the bladder. The bladder neck and ureteral orifices should be inspected for possible damage. Bladder neck injuries must be surgically repaired or patients may experience stress urinary incontinence. Injuries to the ureteral orifices require ureter reimplantation. After formal bladder repair, the urine is diverted using a large-bore Foley catheter and/or suprapubic tube.

SECTION 8

VOIDING DYSFUNCTION

VOIDING DYSFUNCTION

Urinary incontinence affects an estimated 13 million adults in the United States, 85% of whom are women. The problem is especially common among nursing home residents, affecting 50%, and older women, affecting 15% to 30% of women over 65 years old who live in retirement communities. An estimated $15 to $20 billion is spent on this problem each year in the United States alone.

NORMAL ANATOMY OF URINARY CONTINENCE

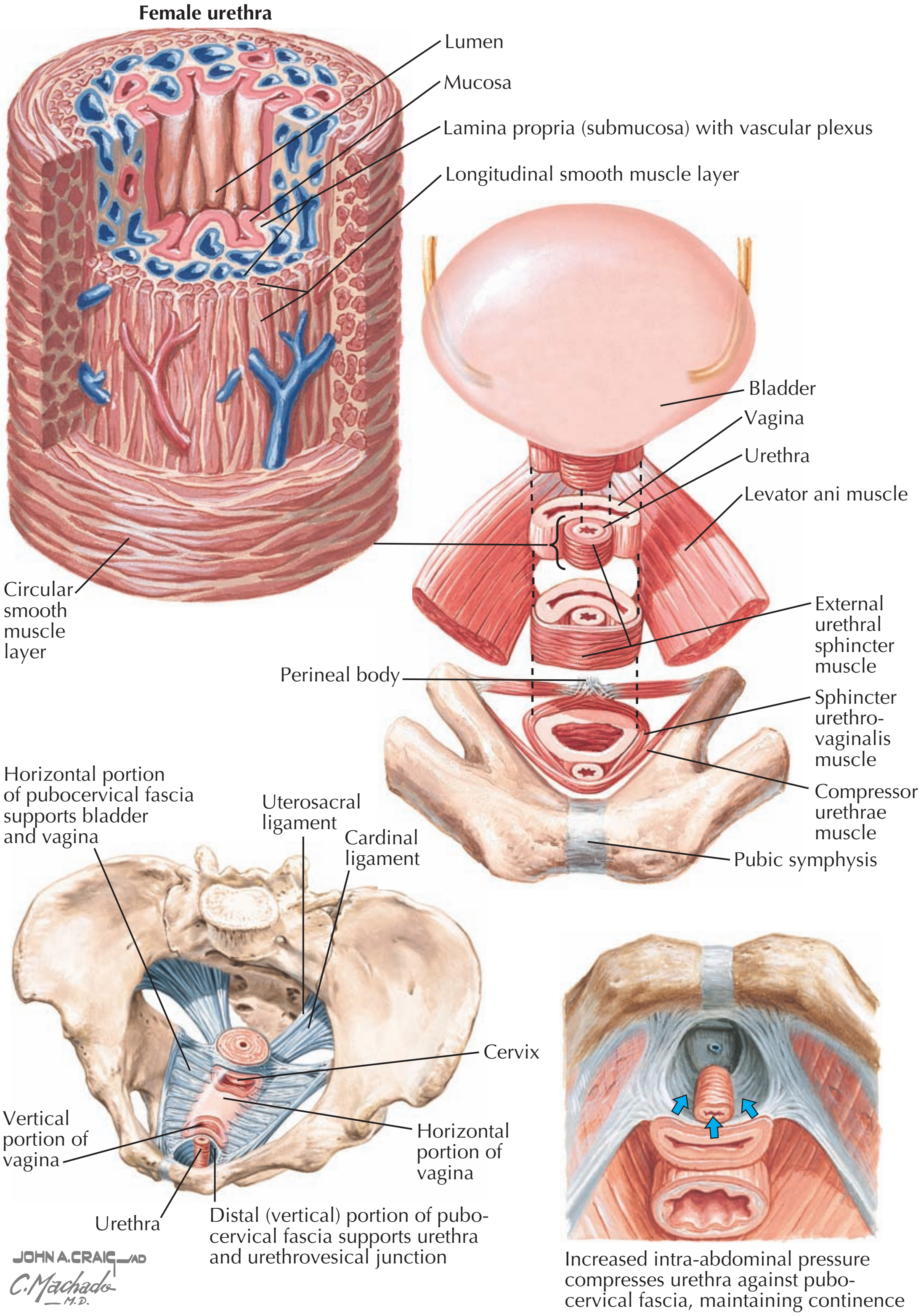
In both sexes, the urethral wall contains smooth muscle cells that constitute an intrinsic urethral sphincter. These cells surround the submucosa and are arranged in an inner longitudinal layer and a thinner outer circular layer.

In males, an internal urethral sphincter is formed by a ring of smooth muscle near the bladder neck, which receives sympathetic input and prevents the retrograde passage of semen during ejaculation.

In both sexes, the urethra is also surrounded by rings of striated muscle that form an external urethral sphincter. In males, this muscle is located around the membranous urethra. In females, it is located primarily around the middle third of the urethra, and it receives fibers from the compressor urethrae and sphincter urethrovaginalis muscles located just above the perineal membrane. The compressor urethrae muscles arise from the ischiopubic rami, with fibers from each side interdigitating anterior to the urethra. Meanwhile, the sphincter urethrovaginalis muscles arise from the perineal body, pass along the lateral walls of the vagina, and then also interdigitate anterior to the urethra.

The pressures exerted by the urethral sphincters alone are sufficient to maintain continence in most circumstances. During acute increases in intraabdominal pressure, however, the proximal urethra requires additional support to resist the resulting increase in intravesical pressure. In females, such support comes from a "hammock" of connective tissue against which the bladder neck and proximal urethra are compressed. The hammock is formed by the pubocervical fascia, which connects to the tendinous arch of the pelvic fascia on each side (which is itself attached to the levator ani muscles).

ANATOMY OF FEMALE URINARY CONTINENCE MECHANISMS


Female urethra
Lumen
Mucosa
Lamina propria (submucosa) with vascular plexus
Longitudinal smooth muscle layer
Circular smooth muscle layer
Bladder
Vagina
Urethra
Levator ani muscle
External urethral sphincter muscle
Perineal body
Sphincter urethrovaginalis muscle
Compressor urethrae muscle
Pubic symphysis
Horizontal portion of pubocervical fascia supports bladder and vagina
Uterosacral ligament
Cardinal ligament
Cervix
Vertical portion of vagina
Horizontal portion of vagina
Urethra
Distal (vertical) portion of pubocervical fascia supports urethra and urethrovesical junction
JOHN A.CRAIG AD
C.Machado M.D.
Increased intra-abdominal pressure compresses urethra against pubocervical fascia, maintaining continence

NEURAL CONTROL OF BLADDER FILLING AND VOIDING

Both filling and voiding require coordinated action of the detrusor muscle and urethral sphincters. During filling, mild distention of the bladder produces afferent signals that travel in pelvic nerves to the spinal cord. These signals trigger spinal reflexes that increase sympathetic outflow along the hypogastric nerves, causing relaxation of the detrusor muscle and contraction of the ureteral smooth muscle. In addition, these reflexes stimulate neurons originating in Onuf nucleus, located in the sacral spinal cord, which travel along the pudendal nerve to stimulate contraction of the external urethral sphincter. This response, known as the "guarding reflex," prevents incontinence during bladder filling.

When bladder distention reaches a set point, intense afferent signals from the bladder activate ascending spinobulbospinal pathways that stimulate the pontine micturition center (PMC, also known as the Barrington nucleus). Activation of the PMC inhibits sympathetic outflow to the bladder and urethra, inhibits pudendal input to the external urethral sphincter, and promotes parasympathetic input to the detrusor along the pelvic splanchnic nerves. The net effect is relaxation of the urethral sphincters followed by contraction of the detrusor, which leads to voiding.

In adults, the PMC can be consciously suppressed until voiding is desired. Such suppression depends on inputs from cortical areas that include the prefrontal cortex, anterior cingulate cortex, and periaqueductal gray. In infants, primitive sacral reflexes promote voiding without the involvement of higher brain areas, such as the PMC. These reflexes eventually become subjected to the control of the PMC and modulatory inputs from the prefrontal cortex.

VOIDING DYSFUNCTION

Voiding dysfunctions reflect abnormalities in either the normal anatomy or neural control of the lower urinary

VOIDING DYSFUNCTION
(Continued)

tract. The major causes of chronic voiding dysfunction can be broadly classified as:

1. Neuropathic dysfunction
2. Stress urinary incontinence
3. Urge urinary incontinence

Of note, overflow incontinence often occurs secondary to neuropathic dysfunction or chronic outlet obstruction, and it is thus not considered a primary form of incontinence.

NEUROPATHIC DYSFUNCTION

Patients with neuropathic dysfunction have aberrations in the neural control of filling and voiding. Lesions at different levels in the relevant neural pathways cause different symptom patterns. Thus the specific level of the lesion must be inferred as precisely as possible based on history and urodynamic data.

With suprapontine lesions (i.e., cerebrovascular accident, Parkinson disease), cortical inhibition of the PMC is eliminated, causing the detrusor to become overactive. Because spinal cord connections remain intact, however, synergy persists between bladder contraction and urethral sphincter relaxation. In Parkinson disease, however, opening of the striated sphincter may be delayed, which could be misinterpreted as dyssynergia.

With lesions of between the pons and spinal cord segment S2 (i.e., multiple sclerosis, trauma), there is initial areflexia of the bladder, but intrinsic spinal reflexes (typically inactive since infancy) slowly emerge and cause the detrusor to become overactive. The voiding is often inefficient, however, because interruption of spinal circuits can lead to detrusor-external sphincter dyssynergia (DESD).

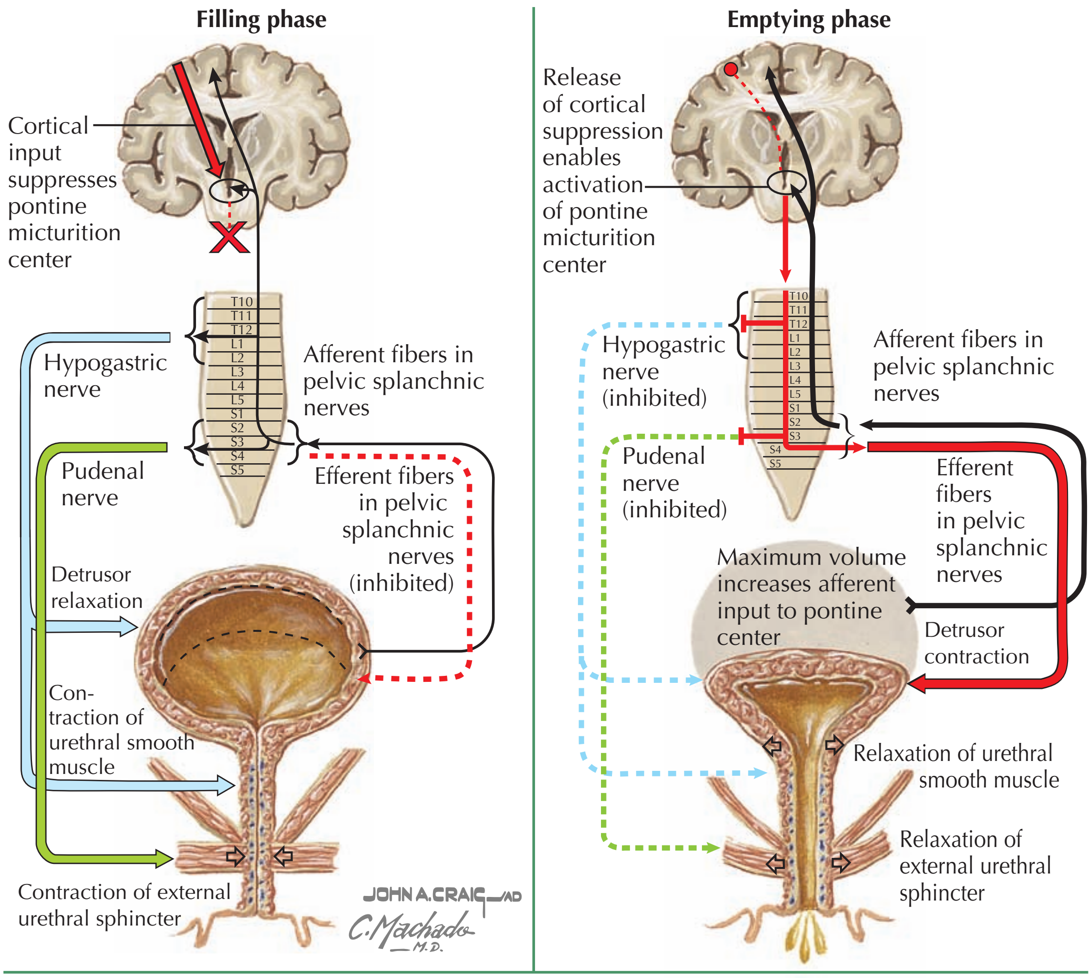
With lesions of the peripheral pelvic nerves (i.e., diabetes mellitus, pelvic surgery), patients lose afferent sensations from the bladder, and the bladder often becomes hypoactive or even areflexic, leading to urinary retention.

A thorough history, neurologic examination, and urodynamic evaluation (see Plate 8-4) often elucidates the specific site of the lesion. The treatment strategy depends on the specific kind of dysfunction.

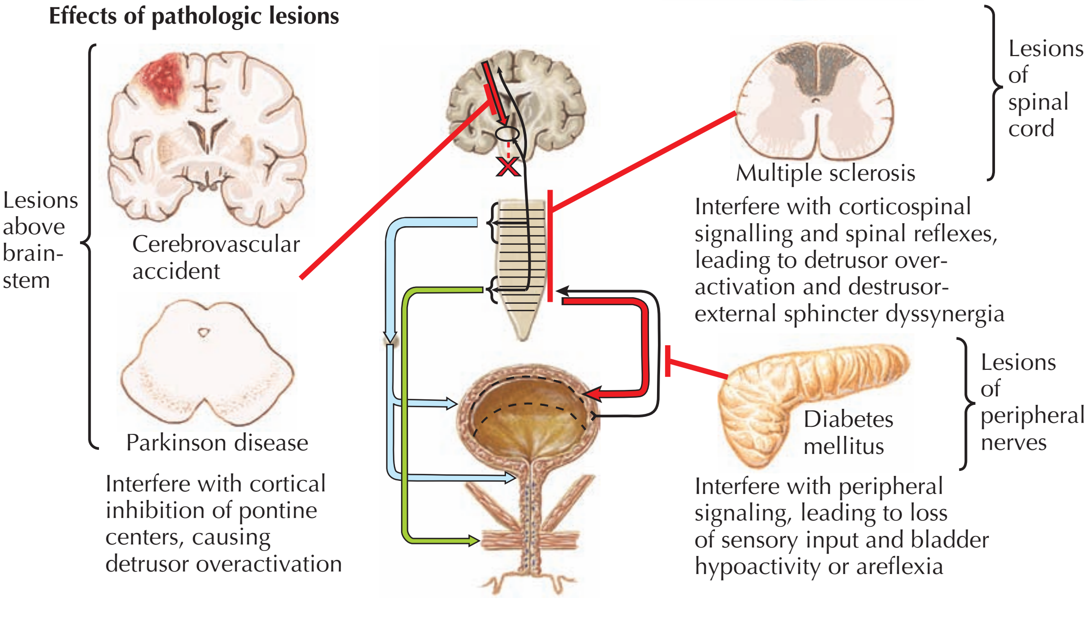
If the detrusor is overactive, pharmacologic agents are the first-line treatment. Anticholinergic drugs, for example, can block parasympathetic input to the bladder. Oxybutynin is a tertiary amine antimuscarinic drug commonly used for this indication; common adverse effects include dry mouth, facial flushing, dry skin, and drowsiness. Tolterodine tartarate is another common agent that generally has fewer adverse effects than oxybutynin. Additional antimuscarinics include solifenacin, darifenacin, trospium, and fesoterodine. In select patients with refractory detrusor overactivity, a sacral nerve stimulator with an implantable electrode can be placed. In others, injection of botulinum toxin into the detrusor muscle may be helpful.

In cases of urinary retention, clean intermittent catheterization is the mainstay of conservative management. Catheterization every 4 to 6 hours can prevent leakage associated with bladder overflow (i.e., overflow incontinence). An indwelling Foley or suprapubic catheter may be required for patients who do not have the manual dexterity or resources to perform clean intermittent catheterization.

NEURAL CONTROL OF BLADDER FILLING AND VOIDING


Filling phase
Cortical input suppresses pontine micturition center
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Hypogastric nerve
Afferent fibers in pelvic splanchnic nerves
Pudenal nerve
Efferent fibers in pelvic splanchnic nerves (inhibited)
Detrusor relaxation
Con-traction of urethral smooth muscle
Contraction of external urethral sphincter
JOHN A.CRAIG AD
C.Machado M.D.
Emptying phase
Release of cortical suppression enables activation of pontine micturition center
Hypogastric nerve (inhibited)
Afferent fibers in pelvic splanchnic nerves
Pudenal nerve (inhibited)
Efferent fibers in pelvic splanchnic nerves
Maximum volume increases afferent input to pontine center
Detrusor contraction
Relaxation of urethral smooth muscle
Relaxation of external urethral sphincter

Effects of pathologic lesions


Lesions above brain-stem
Cerebrovascular accident
Parkinson disease
Interfere with cortical inhibition of pontine centers, causing detrusor overactivation
Lesions of spinal cord
Multiple sclerosis
Interfere with corticospinal signalling and spinal reflexes, leading to detrusor over-activation and destrusor-external sphincter dyssynergia
Lesions of peripheral nerves
Diabetes mellitus
Interfere with peripheral signaling, leading to loss of sensory input and bladder hypoactivity or areflexia

STRESS URINARY INCONTINENCE

As described above, urethral support from the pelvic floor is essential for maintenance of continence during increases in intraabdominal pressure. In response to aging, multiple vaginal deliveries, chronic cough, or obesity, these supports may become damaged or weakened. As a result, the urethra becomes hypermobile and, during episodes of "stress" (i.e., coughing, straining), undergoes rotation and opening that permits leakage of urine. This phenomenon is known as stress urinary incontinence (SUI).

As described previously, the urethral sphincters also protect against incontinence in response to increased intravesical pressure via the guarding reflex. Although these sphincters were once thought to be normal in SUI, it is now known they may exhibit a

VOIDING DYSFUNCTION
(Continued)

variable degree of dysfunction that contributes to urine leakage. Significant dysfunction of the external urethral sphincter may reflect pudendal neuropathy, which can result from aging or prior pregnancy.

A pelvic examination may be remarkable for laxity of the pelvic musculature, while vaginal examination may demonstrate anterior wall weakness, cystocele, or rectocele. During the Valsalva maneuver, urinary leakage may be noted while the patient is in the lithotomy position. The degree of urethral mobility may be assessed by the Q-tip test, in which a well-lubricated, sterile cotton-tipped applicator is inserted into the urethra to the level of the bladder neck. The resting, horizontal angle of the Q-tip and the angle after maximum strain are both recorded. Hypermobility is defined as a resting or straining angle of greater than 30 degrees.

The various treatment options for SUI attempt to restore support to the urethra. Pelvic floor rehabilitation is an intensive program in which patients perform Kegel exercises and other routines to engage and strengthen the pelvic floor. Up to 40% to 50% of patients will be satisfied with the results of this therapy and avoid an operation. Thus noninvasive management should be the first line of therapy for appropriately selected and motivated patients.

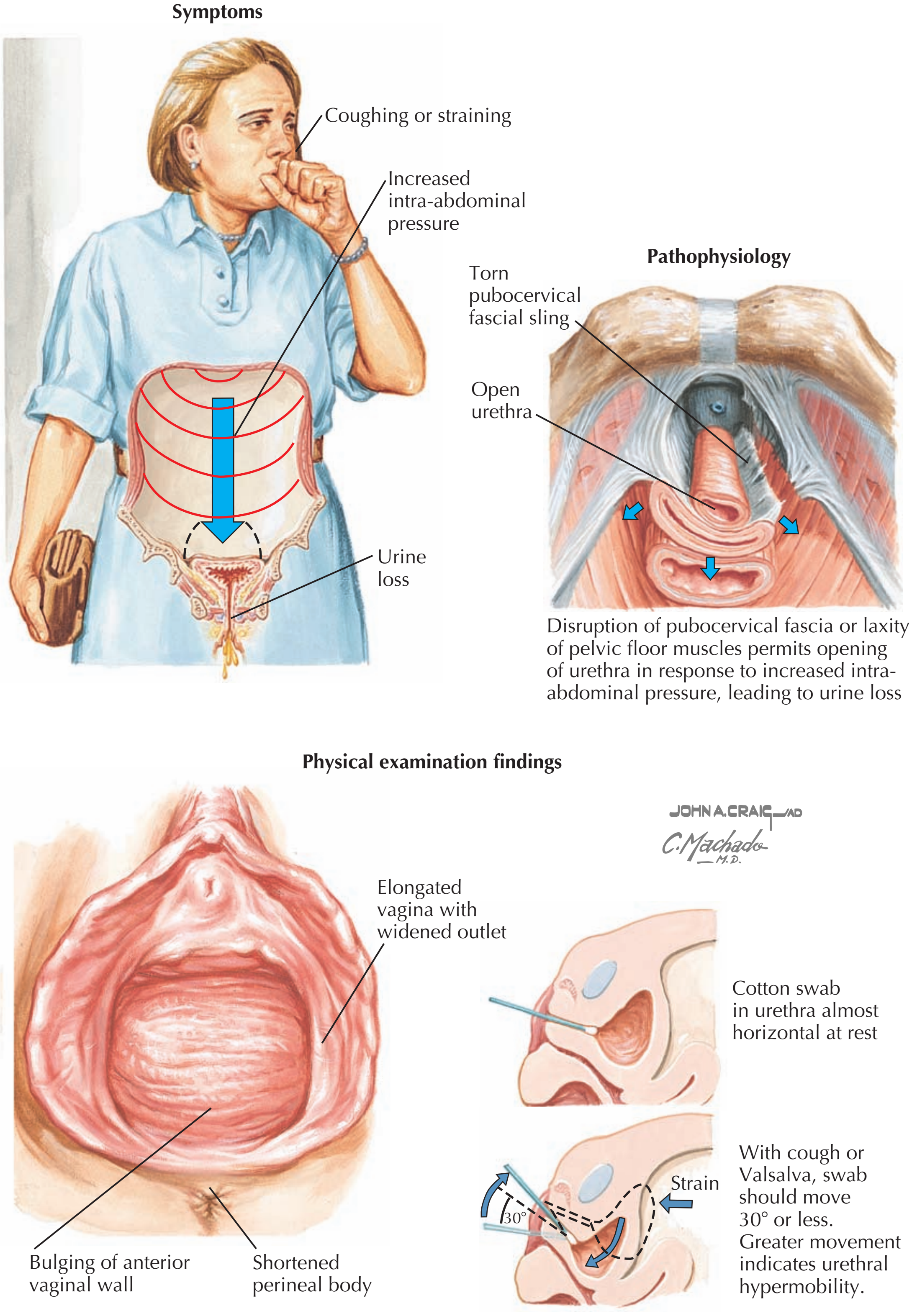
Surgery is indicated in (1) patients with severe symptoms, (2) patients with significant pelvic organ prolapse that may need to be simultaneously corrected, (3) those who are highly motivated to achieve continence because of physical or occupational stress, and (4) those with good pelvic floor function who likely have a significant degree of intrinsic sphincter dysfunction.

Both suprapubic and vaginal approaches have been developed to restore urethral support. In the Marshall-Marchetti-Krantz procedure, which takes a suprapubic approach, the periurethral tissues are attached to the posterior surface of the pubic symphysis. This operation was subsequently modified to become the Burch procedure, in which the anterior vaginal wall is fixed to the Cooper ligament, turning it into a substitute for the normal fascial "hammock" against which the urethra can be compressed.

A vaginal approach is much more common in contemporary times, especially among women with intrinsic sphincteric deficiency or significant pelvic muscle weakness. In one procedure, known as transobturator tension-free vaginal tape, a synthetic piece of polypropylene mesh is passed behind the urethra using a device that crosses through the obturator membranes. In this way, the mesh affords posterior support to the urethra, although its ends are not tethered to the pubic bone. The tape may also be constructed using other organic materials, such as cadaveric fascia lata.

If patients have intrinsic sphincter weakness, injection of bulking material into the urethra is sometimes performed. Such materials include collagen, silicone, or polydimethylsiloxane (solid silicone elastomer).

STRESS URINARY INCONTINENCE


Symptoms
Coughing or straining
Increased intra-abdominal pressure
Urine loss
Pathophysiology
Torn pubocervical fascial sling
Open urethra
Physical examination findings
JOHN A.CRAIG AD
C.Machado M.D.
Elongated vagina with widened outlet
Bulging of anterior vaginal wall
Shortened perineal body
Cotton swab in urethra almost horizontal at rest
Strain
30°
With cough or Valsalva, swab should move 30° or less. Greater movement indicates urethral hypermobility.

Disruption of pubocervical fascia or laxity of pelvic floor muscles permits opening of urethra in response to increased intra-abdominal pressure, leading to urine loss

URGE URINARY INCONTINENCE

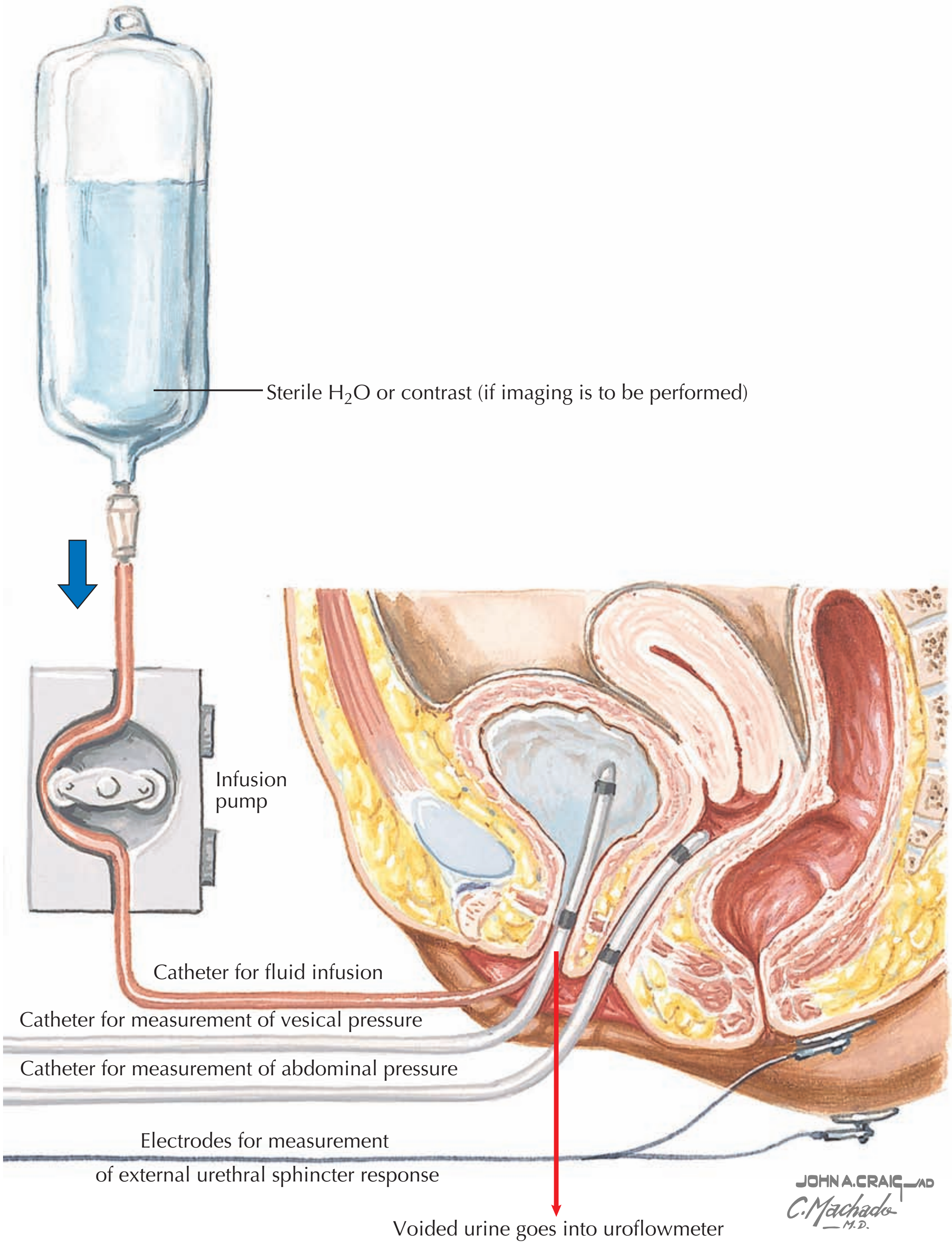
Urge incontinence is typified by the sudden, intense desire to urinate to prevent leakage. In this condition, the detrusor has spontaneous, abnormal contractions, often in the setting of normal anatomy and, in some cases, neural function. Nonneurogenic urge incontinence commonly occurs in patients with cystitis or significant bladder outlet obstruction with a resulting decrease in compliance. The distinction between stress and urge incontinence is important because urge incontinence may result from a secondary pathologic process and is best managed with anticholinergics rather than surgical intervention.

OTHER FORMS OF URINARY INCONTINENCE

Although not as prevalent as the forms of incontinence described previously, other mechanisms of urinary incontinence may occur. Fistulous communication between the bladder and the vagina or rectum, commonly a result of prior surgery or neoplasm, can result in total incontinence.

Surgical damage to the urinary sphincter may also result in incontinence. Finally, among the pediatric population, incontinence may result from ectopic ureteral insertion or urethral attachments, as well as other urogenital anomalies that affect the development of the external sphincter, such as epispadias.

Equipment and Set-up for Urodynamic Studies


Sterile H_2O or contrast (if imaging is to be performed)
Infusion pump
Catheter for fluid infusion
Catheter for measurement of vesical pressure
Catheter for measurement of abdominal pressure
Electrodes for measurement of external urethral sphincter response
Voided urine goes into uroflowmeter
JOHN A.CRAIG AD
C.Machado M.D.

URODYNAMICS

Urodynamic testing is an important part of the evaluation of voiding dysfunction. Urodynamic studies (UDS) use pressure-flow studies and electromyography to evaluate bladder, urethral, and pelvic floor muscle function while simultaneously integrating real-time, subjective sensations experienced by the patient.

There are numerous indications for UDS, which include:

1. Patients with recurrent incontinence, in whom surgery is planned
2. Patients with a mix of stress and urge incontinence
3. Patients with neurologic disorders and voiding dysfunction
4. Patients with lower urinary tract symptoms suggestive of bladder outlet obstruction

SET-UP

The patient is seated. For the first part of the examination, known as uroflowmetry, the patient freely and spontaneously voids into a uroflowmeter. For the remaining components of the examination, one or more catheters are placed in the bladder to measure intravesical pressure and infuse contrast, while another catheter is placed in the rectum or vagina to measure intraabdominal pressure. An image intensifier is positioned over the patient's pelvis to obtain fluoroscopic views of the bladder. Finally, a patch or needle electrode may be placed near the external urethral sphincter or external anal sphincter to measure activation potentials. Although both locations generally give similar recordings, the former is considered more accurate.

COMPONENTS OF THE EXAMINATION

Uroflowmetry. Uroflowmetry provides a graphic analysis of urine flow rate over time. For the reading to be valid, a minimum of 150 mL of urine should be voided. The normal flow shape is a bell-shaped curve, in which the rate rapidly rises, plateaus, and then declines. Several values can be calculated from the curve, including total voided volume, total void time, maximum flow rate, and average flow rate (total voided volume/total void time). The normal average flow rate from a full bladder is about 20 to 25 mL/sec in men and 25 to 30 mL/sec in women, although these values can vary depending on the volume voided and patient age.

Because urinary flow is the result of detrusor pressure against outlet resistance, abnormalities may reflect dysfunction in either of these units. Findings suggestive of obstruction include a low average or maximum urine flow rate (less than 10 mL/sec), prolonged void time, or a syncopated pattern of flow (indicating the subject needs to restore adequate intraabdominal pressure to sustain flow).

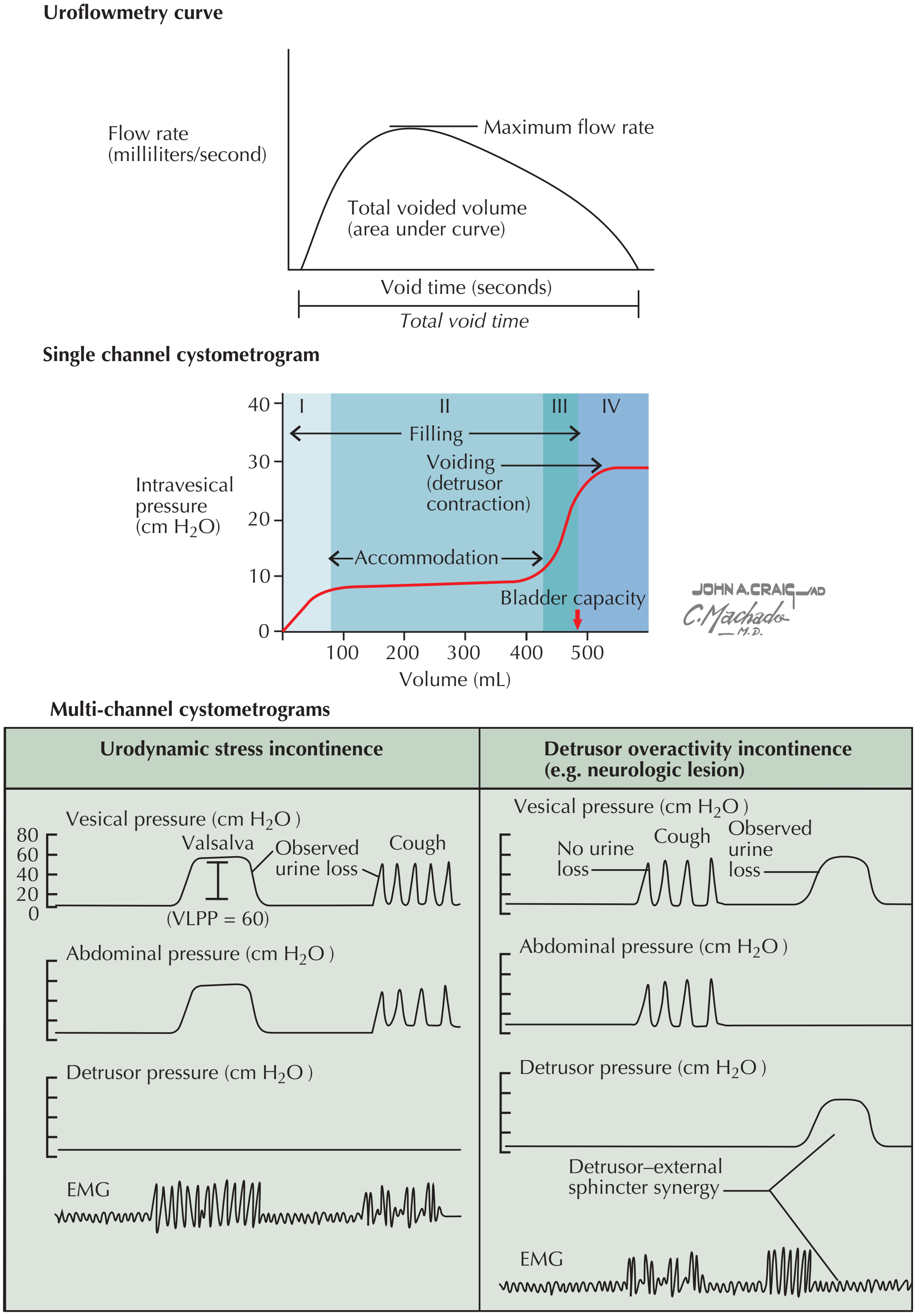
Normal flow patterns may occur even in the presence of voiding abnormalities if compensatory mechanisms have developed. For example, a low detrusor pressure may be associated with normal flow rates if there is compensatory low outlet resistance or high intraabdominal pressure. Likewise, high detrusor pressures may overcome an outlet obstruction. The use of pressure-flow studies, described later, can unmask such abnormalities.

Cystometry. In cystometry, fluid is infused into the bladder while intravesical and intraabdominal pressure is documented using urethral and vaginal or rectal catheters. Detrusor pressure is calculated by subtracting intraabdominal pressure from intravesical pressure.

A single-channel cystometrogram documents intravesical pressure as a function of the volume of fluid infused. Four phases are seen. The first three phases represent bladder filling. The first phase contains a sharp initial rise in pressure as fluid is first infused. The second phase, known as the tonus limb, features a smaller rise in pressure as additional fluid is infused, and it reflects accommodation of the elastic bladder wall. The third phase contains a more dramatic rise in pressure that occurs as the bladder wall becomes maximally distended. The fourth phase is the voiding phase, which occurs when the bladder has reached its maximum capacity. Throughout this process, patients are asked to comment on the sensation at first filling and when they experience both their first desire to void and a strong desire to void. The volumes at which patients experience these sensations are noted.

UKRODYNAMICS *(Continued)*

Sample Urodynamic Recordings



Several metrics can be determined based on a single-channel cystometrogram. Bladder compliance, for example, can be determined by noting the intravesical pressure and volume at the start of the study and at the end of the filling phase, then dividing the volume change by the pressure change. A normal bladder compliance is less than 12.5 mL/cm H_2O. Involuntary and sudden increases in pressure during the filling phase suggest an overactive detrusor. Bladder capacity, normally 300 to 500 mL, may be determined by measuring the volume at which the patient has a strong desire to void and cannot comfortably tolerate further infusion of contrast.

A multichannel cystometrogram documents intravesical pressure, intraabdominal pressure, detrusor pressure, urine flow, infused volume, and EMG potential as a function of time. By examining all of these variables simultaneously, additional metrics can be determined, such as the Valsalva leak point pressure (VLPP), which is used to assess for SUI. The VLPP is equal to the abdominal pressure sustained during a Valsalva maneuver that causes urine to leak around the urethral catheter in the absence of detrusor contraction or a cystocele. A VLPP less than 60 cm H_2O suggests SUI because of intrinsic sphincter dysfunction, whereas VLPP more than 90 cm H_2O suggests SUI because of urethral hypermobility. Values between 60 and 90 cm H_2O suggest mixed causes. In patients without stress urinary incontinence, there is no VLPP at physiologic filling.

The detrusor leak point pressure (DLPP) is the pressure at which urine leaks around the catheter independent of detrusor contraction or the Valsalva maneuver. DLPP is clinically significant because very high pressure (i.e., in excess of 40 cm H_2O) suggests pressure is being transmitted to the upper urinary tract, increasing the risk of hydronephrosis and eventual renal atrophy.

Pressure Flow Studies. Pressure flow studies use a combination of the above modalities to examine the relationship between urine flow and detrusor pressure during emptying. For example, in patients with low urinary flow rates, high detrusor pressure suggests an outlet obstruction, whereas low detrusor pressure suggests detrusor hypocontractility.

Electromyography (EMG). EMG of the external urethral sphincter can help determine if there is coordination or discoordination with the detrusor muscle. At the beginning of cystometry, before bladder filling begins, the patient is asked to demonstrate volitional control of the sphincter by actively contracting and relaxing this muscle. The ability to do so indicates intact pyramidal tracts. The bulbocavernosus reflex may also be tested by squeezing the glans penis or clitoris, or by pulling on the bladder catheter. A burst of EMG activity, signifying a positive result, implies an intact sacral arc.

During micturition, the sphincter should relax. If it does not, and a neurologic lesion is likely to be present, this abnormality is termed detrusor–external sphincter dyssynergia (DESD). It typically occurs because of lesions between the pons and sacral spinal cord, with interruption of the fibers that normally coordinate the detrusor and the urethral sphincter. If patients do not have evidence of a neurologic lesion, the term pelvic floor hyperactivity or dysfunctional voiding is used instead of DESD.

Cystogram. A cystogram, obtained using real-time fluoroscopic imaging, may be performed during urodynamics to provide real-time anatomic correlates to filling or voiding. This imaging modality provides a visual correlate to the volume instilled, captures the appearance of the bladder and bladder neck during filling and voiding, and demonstrates whether vesicoureteral reflux (VUR) if present.

Residual Urine. The postvoid residual (PVR) is determined by catheterization, ultrasound, or cystogram at the end of a voiding event. A high PVR (>150 cc) is suggestive of bladder outlet obstruction or poor detrusor contractility.

SECTION 9

NEOPLASMS

BENIGN RENAL TUMORS

There are several different kinds of benign renal tumors, which may originate from a wide range of cell types. Solid renal tumors, however, are generally malignant, with the probability of malignancy strongly correlating with tumor size. For example, one series found that masses greater than 4 cm in diameter were malignant in more than 90% of cases, whereas those less than 1 cm in diameter were malignant in 54% of cases. Although certain benign tumors have characteristic radiologic findings, most cannot be distinguished from malignant tumors using imaging alone. Thus most solid masses are surgically removed, with the final diagnosis rendered only after histopathologic examination. Some of the more common and well-documented benign renal tumors are presented here.

PAPILLARY ADENOMA

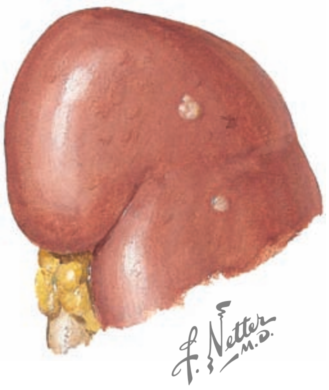
Small cortical lesions are seen in 7% to 23% of kidneys at the time of autopsy. These are defined as papillary adenomas by the World Health Organization Classification of Tumours when they possess papillary or tubular architecture of low nuclear grade and are 5 mm or smaller in diameter. These masses are too small to be reliably detected using modern imaging techniques.

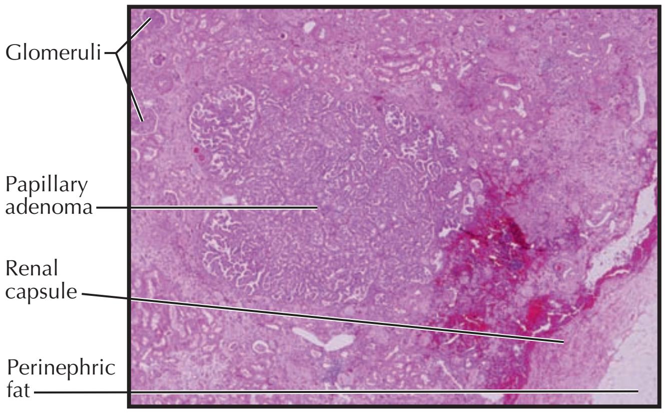
ONCOCYTOMA

Oncocytomas account for approxmately 5% of renal tumors in adults. They are often incidental findings, occurring most commonly in those over the age of 50. They are believed to originate from the intercalated cells of the collecting duct. Classic radiographic features include a central stellate scar on CT imaging and a spoke-wheel pattern of blood vessels on angiography; however, these findings are unreliable and frequently absent, and angiography is now rarely performed as part of the diagnostic workup. Thus oncocytomas cannot reliably be distinguished from malignant tumors using noninvasive methods. Biopsies, however, are also unreliable because oncocytoma-like areas can be found in chromophobe renal cell carcinomas. Thus even a suspected oncocytoma is generally treated like a renal cell carcinoma, with the definitive diagnosis established only after surgical resection of the entire mass. Grossly, the tumors appear well-circumscribed and mahogany brown, with a central stellate scar seen in about one third of cases. There may be small areas of hemorrhage, but necrosis should not be seen. Characteristic histopathologic findings include round to polygonal cells that have strongly eosinophilic cytoplasm and round nuclei, and which are arranged in nests, acini, tubules, and microcysts.

PAPILLARY ADENOMA AND ONCOCYTOMA

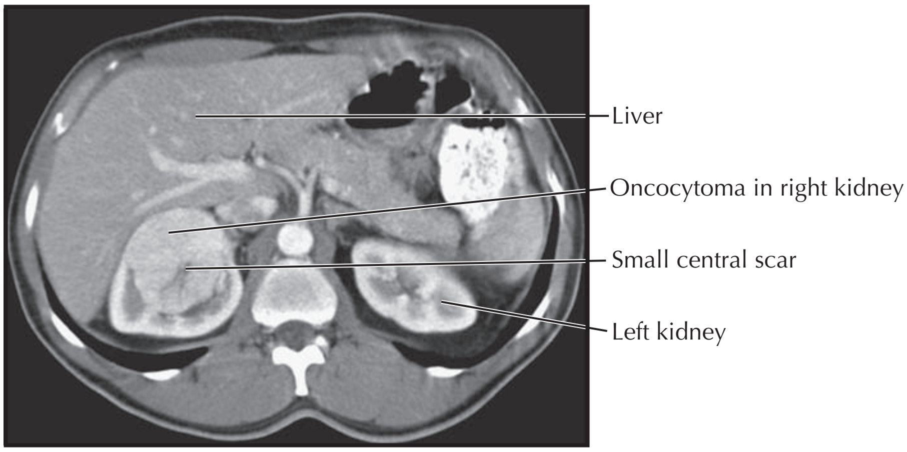
Papillary adenoma



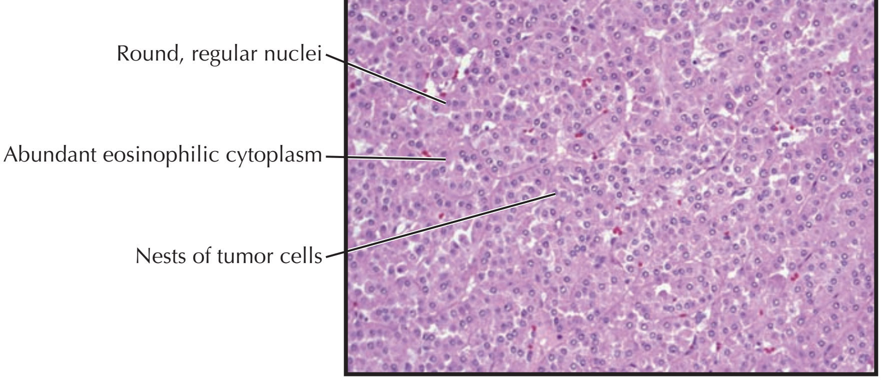


H and E stain

Oncocytoma



Computed tomography (contrast-enhanced)



H and E stain

ANGIOMYOLIPOMA

Angiomyolipoma (AML) of classic type are benign mesenchymal neoplasms composed of blood vessels, smooth muscle, and adipose tissue. (There are rare AMLs of epithelioid type that can exhibit malignant behavior.) About half of AMLs occur in otherwise healthy individuals, generally in their fifth or sixth decade. Most of the remainder occur in those with the genetic disorder known as tuberous sclerosis (TS), which has numerous manifestations affecting multiple organ systems. Besides renal AML, the other major clinical features of TS include cerebral cortical tubers; subependymal nodules; retinal hamartomas; cardiac rhabdomyomas; facial angiofibromas, typically in a malar distribution (formerly known as adenoma sebaceum); hypopigmented macules known as ash-leaf spots; orange peel-like plaques on the lower back known as shagreen patches; and periungual fibromas (flesh colored papules near the fingernail bed). 70% to 80% of patients with tuberous sclerosis develop renal AMLs, typically in their fourth decade. Benign renal cysts may also be seen.

Like other renal tumors, AMLs are often discovered as incidental findings on axial imaging. Less commonly, the tumors may cause flank pain, hematuria, and a palpable abdominal mass. In rare cases, life-threatening retroperitoneal hemorrhage may occur, a phenomenon known as Wunderlich syndrome. AMLs can often be distinguished from other renal masses using computed tomography (CT) because their fat content causes them to appear as hypoattenuating lesions (less than −20 Hounsfield units). The presence of fat, however, is not pathognomonic for AML, since certain primary renal sarcomas (such as liposarcoma) and rare renal cell carcinomas may also contain fat. In addition, AMLs sometimes have little fat content that cannot be visualized with CT imaging.

The optimal management of an AML depends on tumor size and associated symptoms. Lesions that are more than 4 cm in diameter or that cause pain or hematuria are managed with embolization or extirpation (with a nephron-sparing technique whenever possible).

BENIGN RENAL TUMORS

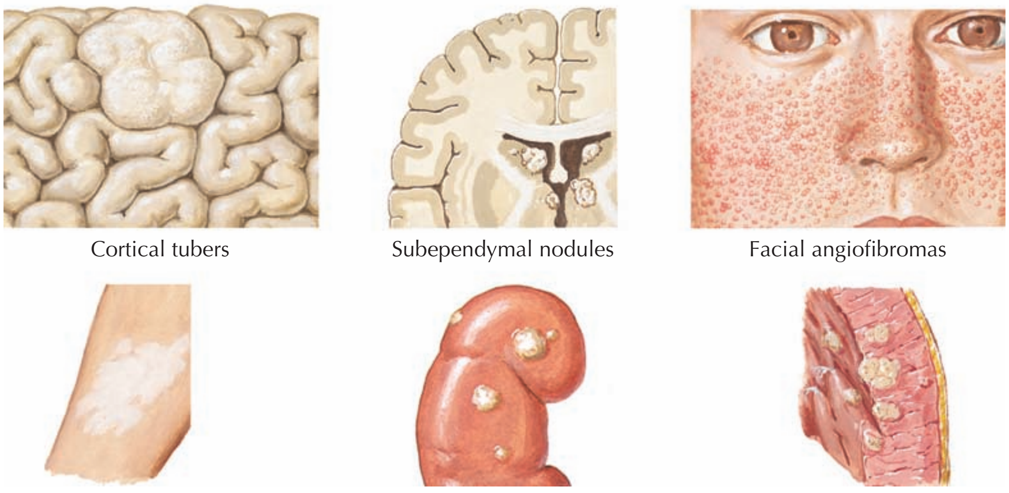
(Continued)

Fat-poor tumors that cannot be confidently distinguished from renal cell carcinoma should also be removed. In contrast, patients with smaller, asymptomatic lesions that strongly resemble AML can be monitored with serial imaging studies at 6- to 12-month intervals.

Grossly, an AML is typically solid and well circumscribed, although it is not encapsulated. Patients with sporadic AML tend to have a single, large mass, whereas those with TS tend to have multiple, small masses. Microscopically, the mature adipose tissue varies in amount: in some cases it constitutes most of the tumor, whereas in others only rare adipocytes are present. The blood vessels have abnormally thick walls. The smooth muscle cells may be spindled and grow in bundles or epithelioid with abundant eosinophilic cytoplasm. Immunohistochemical stains are often valuable, especially in small needle biopsy samples. The smooth muscle cells express both smooth muscle markers (smooth muscle actin and h-caldesmon) and melanocytic markers (such as HMB-45 and Melan-A), and they are negative for epithelial markers (cytokeratin).

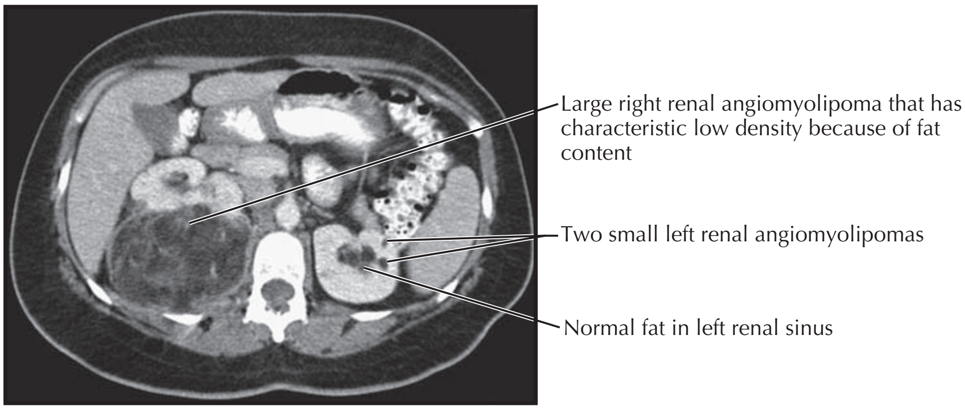
ANGIOMYOLIPOMA

Common manifestations of tuberous sclerosis

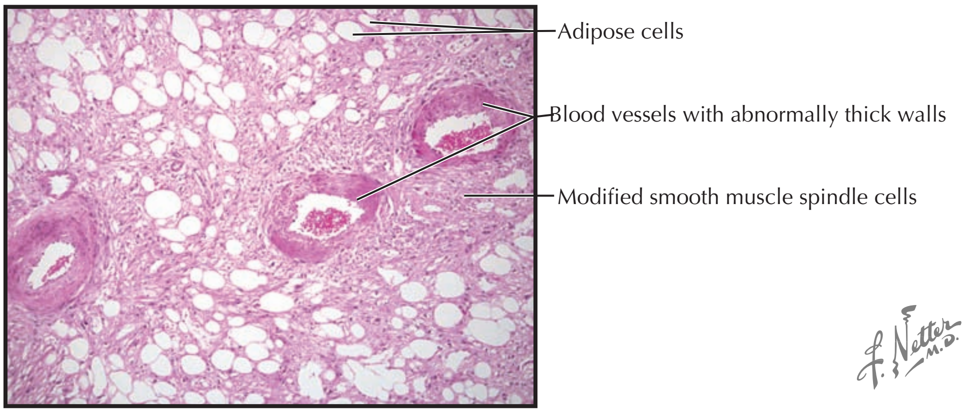


Cortical tubers | Subependymal nodules | Facial angiofibromas

Hypopigmented macules | Renal angiomyolipomas | Cardiac rhabdomyomas


Large right renal angiomyolipoma that has characteristic low density because of fat content
Two small left renal angiomyolipomas
Normal fat in left renal sinus

Computed tomography (contrast-enhanced)


Adipose cells
Blood vessels with abnormally thick walls
Modified smooth muscle spindle cells

H and E stain

CYSTIC NEPHROMA

Cystic nephromas, sometimes called multilocular cystic nephromas, are benign tumors most often discovered in women in their fourth or fifth decade. They should be distinguished from cystic nephromas in children, which are considered to be differentiated Wilms tumors. On axial imaging, cystic nephromas are well-circumscribed and contain multiple noncommunicating, fluid-filled cystic spaces and no calcifications. Thus, they resemble category III or IV cysts according to the Bosniak classification scheme (see Plate 2-14), raising concern for renal cell carcinoma. As a result, they are usually surgically resected with either a radical or partial nephrectomy, depending on size and location. On histopathologic examination, the septa consist of fibrous tissue lined by cuboidal cells that may show hobnail features and flattening.

METANEPHRIC ADENOMA

Metanephric adenomas are rare benign tumors that are often incidental findings in middle aged individuals, with a higher incidence among women than among men. Like other renal tumors, they occasionally cause hematuria, abdominal or flank pain, and a palpable abdominal mass. They may also cause secondary polycythemia. They resemble renal cell carcinomas on axial imaging, and it is often difficult to distinguish between the two. Thus these masses are usually surgically resected, with the definitive diagnosis established on histopathologic analysis. Grossly, most metanephric adenomas are 3 cm to 6 cm in diameter, and they are usually solid with gray to tan to yellow cut surfaces. The histopathologic findings include closely packed small, uniform round acini composed of small bland nuclei. Psammoma bodies may be seen.

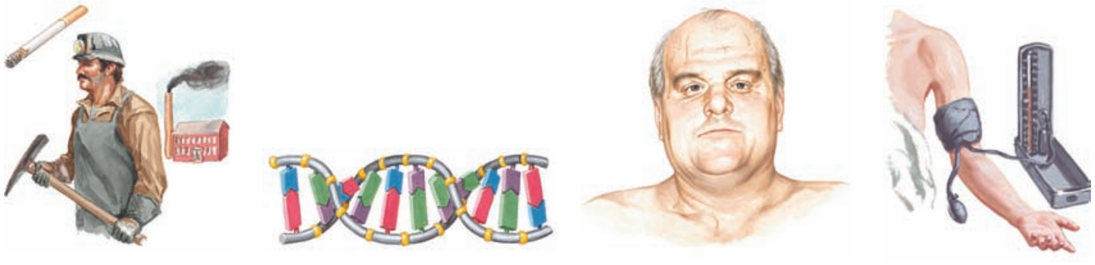
ADDITIONAL BENIGN MESENCHYMAL NEOPLASMS

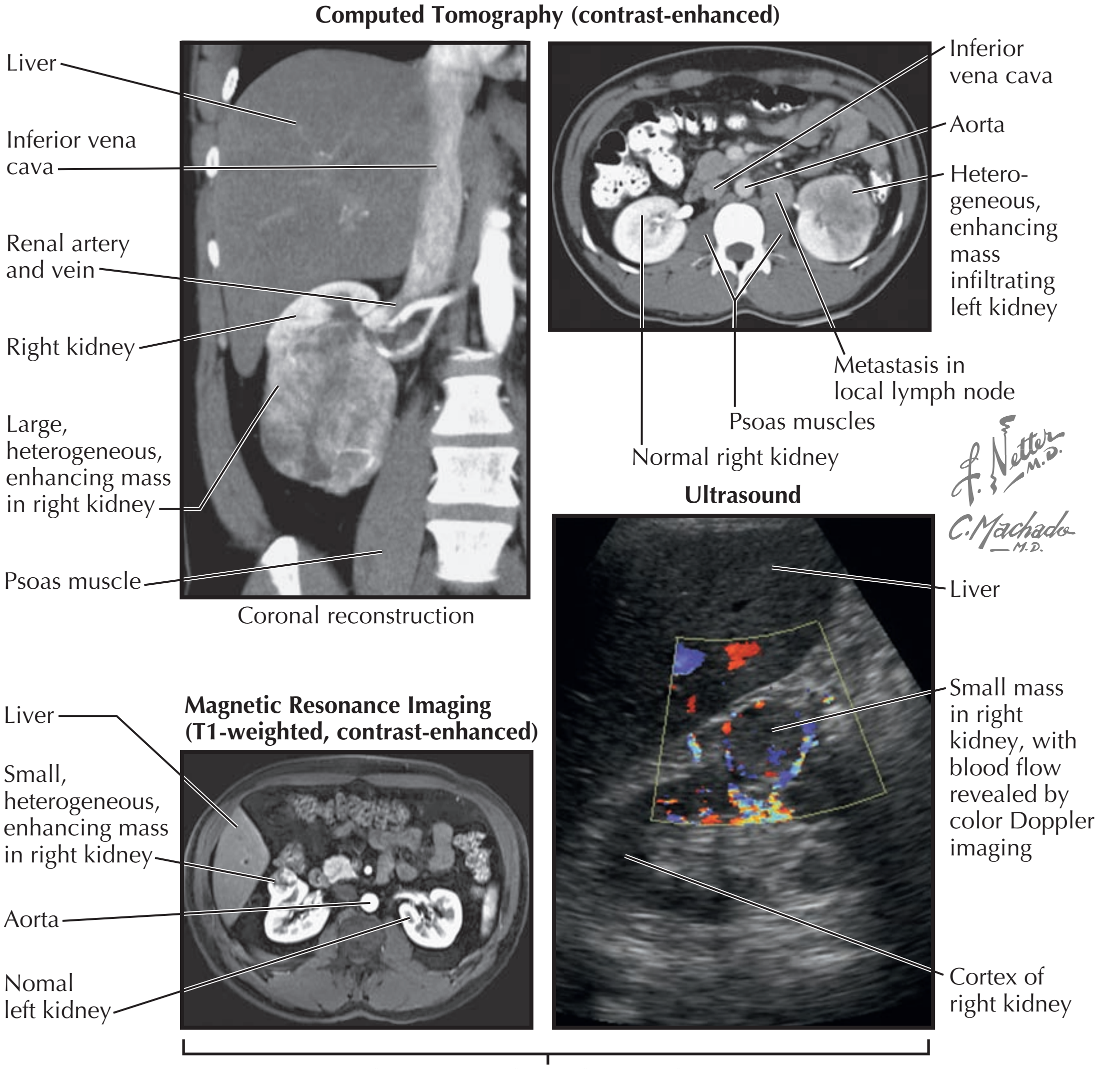
In addition to AML, several other benign mesenchymal renal neoplasms have been reported in the kidney, including juxtaglomerular cell tumor, leiomyoma, hemangioma, lymphangioma, schwannoma, lipoma, solitary fibrous tumor, myxoma, and neurofibroma.

Juxtaglomerular Tumor (Reninoma). Juxtaglomerular tumors are rare, benign, renin-secreting masses derived from the juxtaglomerular apparatus. The classic presentation is a young patient (<25 years) with headache and hypertension who is found to have elevated serum renin and aldosterone concentrations and a low serum potassium concentration. Most tumors are unilateral, solitary, and relatively small (2 to 3 cm). Treatment consists of surgical removal, preferably with nephron-sparing surgery. Grossly, these tumors are well-encapsulated, with tan to yellow solid cut surfaces. Microscopically, the appearance is quite variable, with many tumors showing sheets of uniform round cells.

Renal Hemangioma. Renal hemangiomas are rare benign lesions that may cause either microscopic or gross hematuria. Most lesions are small and cannot be visualized using routine axial imaging of the kidney. Historically, arteriography was the most sensitive imaging modality; however, most renal hemangiomas are now diagnosed using cystoscopy, in which patients are noted to have unilateral hematuria (i.e., gross blood emerging from only one ureteric orifice). Most hemangiomas are located at the tip of a papilla and can range in size from pinpoint to several centimeters in diameter. In the past these masses were treated with nephrectomy or embolization; at present, however, treatment is usually electrocautery or laser ureteroscopic ablation.

Risk Factors and Radiographic Findings of Renal Cell Carcinoma


Carcinogen exposure
• Cigarettes
• Cadmium
• Asbestos
• Petroleum by-products
Inherited genetic mutations
• Von Hippel-Lindau disease
• Hereditary papillary RCC
• Birt-Hogg-Dube syndrome
• Others
Obesity
Hypertension


Computed Tomography (contrast-enhanced)
Liver
Inferior vena cava
Renal artery and vein
Right kidney
Large, heterogeneous, enhancing mass in right kidney
Psoas muscle
Coronal reconstruction
Inferior vena cava
Aorta
Hetero-geneous, enhancing mass infiltrating left kidney
Metastasis in local lymph node
Psoas muscles
Normal right kidney
Ultrasound
Liver
Small mass in right kidney, with blood flow revealed by color Doppler imaging
Cortex of right kidney
Magnetic Resonance Imaging (T1-weighted, contrast-enhanced)
Liver
Small, heterogeneous, enhancing mass in right kidney
Aorta
Nomal left kidney

These images depict the same lesion

RENAL CELL CARCINOMA

Renal cell carcinomas (RCC) account for a vast majority of primary malignant renal tumors. Approximately 55,000 new cases are diagnosed in the United States each year, and about one third of patients have metastatic disease. Other, less common malignant renal tumors include transitional cell carcinomas of the renal pelvis (see Plate 9-9) and primary renal sarcomas. The kidneys may also contain metastases from extrarenal solid and hematologic tumors.

EPIDEMIOLOGY AND RISK FACTORS

RCC was once more than twice as common among men than among women, although this gap currently appears to be shrinking. The peak incidence is in the sixth to seventh decades of life. Environmental risk factors include cigarette smoking and exposure to cadmium, asbestos, or petroleum byproducts. Data suggest that cigarette smoking and cadmium exposure each double the risk, and that smoking alone is responsible for one third of total cases. In addition, genetic abnormalities in critical tumor suppressor genes and oncogenes are known to play a key role. Such mutations can be sporadic or part of a hereditary condition, such as von Hippel-Lindau disease, hereditary papillary RCC, and Birt-Hogg-Dube syndrome. Hypertension and obesity also increase the risk for RCC, although the mechanisms are not known. Although many tumors occur in patients without known risk factors, it is likely that a significant number of “sporadic” cases will eventually be found to have a genetic basis.

PRESENTATION, DIAGNOSIS, AND STAGING

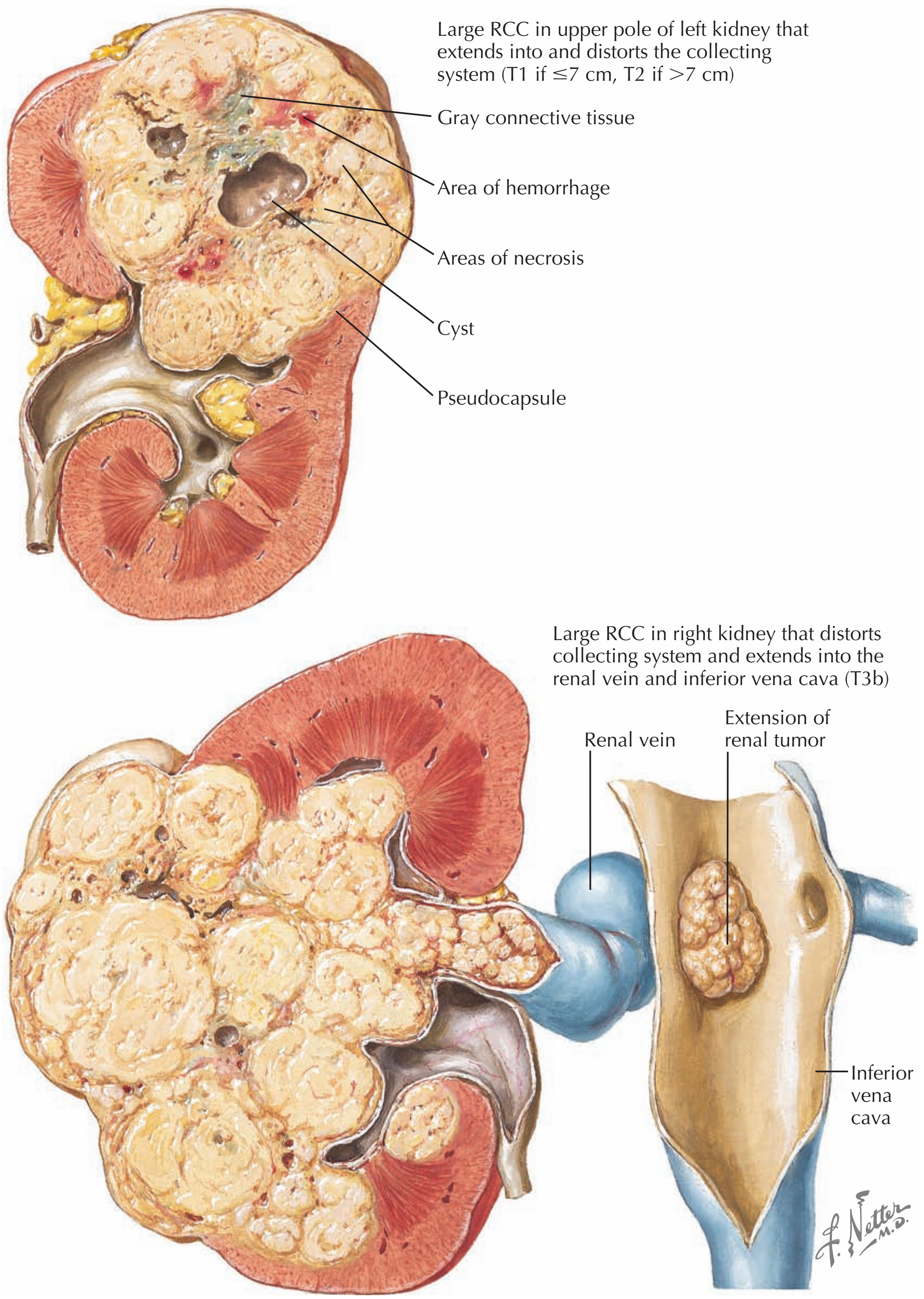
In the past, an RCC was typically not detected until it became symptomatic, usually as the classic triad of gross hematuria, flank pain, and a palpable mass. In contemporary practice, however, the classic triad is seen in fewer than 10% of patients. Instead, the majority of renal masses are now incidentally detected during abdominal imaging.

Nonetheless, an RCC may also cause a variety of nonspecific symptoms, including weight loss, fever, night sweats, and lymphadenopathy. Some patients may also have dyspnea, cough, and bone pain, which are suggestive of metastatic disease. Finally, RCC can also be associated with a wide variety of paraneoplastic phenomena, including erythrocytosis, anemia, hypercalcemia, hypertension, and nonmetastatic hepatic dysfunction (Stauffer syndrome). Patients with any combination of these symptoms or syndromes require immediate evaluation for possible RCC.

The evaluation of a known or suspected RCC begins with a thorough history and physical examination, with careful attention to the symptoms listed previously. On laboratory assessment, possible abnormalities include abnormal hematocrit, elevated erythrocyte sedimentation rate, elevated serum calcium concentration, and abnormal liver function tests. Finally, a careful evaluation of kidney function is important because it may have a significant impact on the type of management if RCC is diagnosed. A normal serum creatinine concentration is an acceptable assessment of renal function in patients with no comorbidities and normal-appearing kidneys on standard axial imaging. In patients with medical conditions that predispose to renal disease, such as hypertension and diabetes mellitus, assessing the function of each kidney with a nuclear scan may be helpful for deciding between radical and nephron-sparing approaches.

Several imaging techniques may be used to evaluate a suspected RCC, including ultrasound (US), computed

GROSS PATHOLOGIC FINDINGS IN RENAL CELL CARCINOMA


Large RCC in upper pole of left kidney that extends into and distorts the collecting system (T1 if ≤7 cm, T2 if >7 cm)
Gray connective tissue
Area of hemorrhage
Areas of necrosis
Cyst
Pseudocapsule
Large RCC in right kidney that distorts collecting system and extends into the renal vein and inferior vena cava (T3b)
Renal vein
Extension of renal tumor
Inferior vena cava
F. Netter M.D.

RENAL CELL CARCINOMA

(Continued)

tomography (CT), magnetic resonance imaging (MRI), renal angiography, and radionuclide imaging (renography).

CT scan is the most frequently employed modality because it has a high sensitivity for detecting renal masses and is the most accurate. Any renal mass that enhances with contrast is potentially malignant. CT also provides excellent visualization of the adjacent structures into which the primary tumor can extend or metastasize—such as the renal vein, regional lymph nodes, inferior vena cava, and suprarenal (adrenal) glands—which enables accurate staging.

Ultrasound can help identify the presence of a renal mass. Although ultrasound evaluation does not require ionizing radiation and is less expensive than CT, it is less sensitive and is highly dependent on operator skill.

MRI is as sensitive as CT and is the study of choice for patients who cannot receive iodinated contrast.

The most common sites for metastasis of renal cell carcinoma include the local and thoracic lymph nodes, lungs, liver, bone, brain, ipsilateral suprarenal gland, and contralateral kidney. Thus metastatic evaluation should include a chest radiograph/CT scan and liver function tests. Bone scans may be indicated if the patient complains of musculoskeletal pain, or if the serum calcium or alkaline phosphatase concentrations are elevated.

Renal tumors are generally not biopsied because of concerns regarding complications, the false-negative result rates, and the fact that an overwhelming majority (>90%) of renal masses greater than 4 cm in diameter are malignant. In contemporary practice, with more small renal tumors (<4 cm) being identified, the role of renal biopsy is actively being reevaluated, and it is likely that in the future renal biopsy will become a more common practice. Potential complications include bleeding, infection, needle track seeding, and pneumothorax. In addition, false negatives for malignancy do occur.

TREATMENT

The optimal treatment of RCC depends largely on the tumor stage, size, and location, as well as the patient's overall clinical condition.

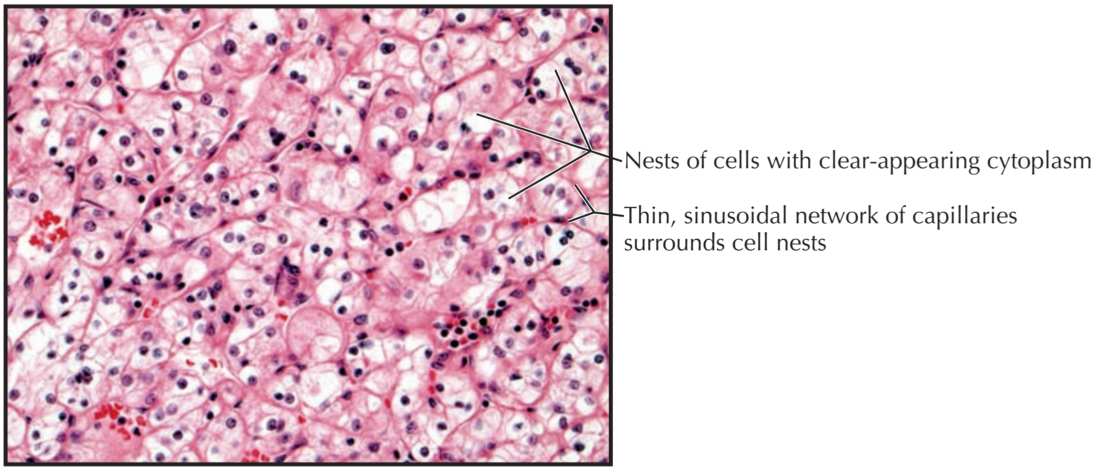
Localized disease can be surgically treated with radical resection (see Plate 10-19), nephron-sparing surgery (such as partial nephrectomy [see Plate 10-22] or ablation [see Plate 10-24]), or observation with an active surveillance protocol. In contrast, unresectable or metastatic RCC in patients with good functional status is commonly managed with initial cytoreductive surgery followed by systemic medications, such as interleukin 2 and tyrosine kinase inhibitors. In patients with poor functional status, medical therapy alone is used.

Localized Disease. Radical nephrectomy was previously the initial standard of care for the treatment of all localized RCCs. The operation involves complete removal of the kidney and suprarenal (adrenal) gland within the renal fascia, as well as removal of regional lymph nodes from the crus of the diaphragm to the aortic bifurcation. The surgery can be performed using either an open or laparoscopic approach and results in an extremely low local recurrence rate (2% to 3%). Laparoscopic radical nephrectomy, however, has become increasingly popular in recent years because of shorter recovery times and equivalent oncologic outcomes when compared with the open approach. Thus it is now considered the treatment of choice for patients with localized tumors less than 10 cm in diameter with no local invasion, renal vein involvement, or lymph node metastasis.

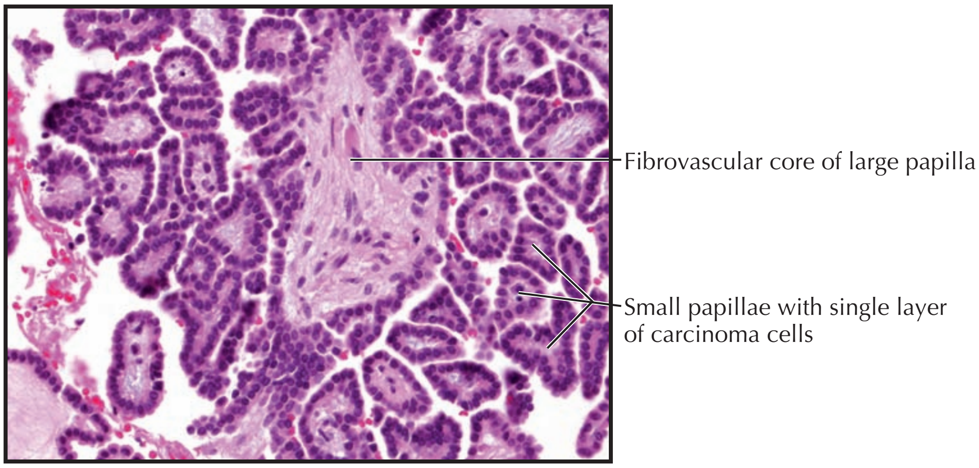
RENAL CELL CARCINOMA
(Continued)

HISTOPATHOLOGIC FINDINGS IN RENAL CELL CARCINOMA

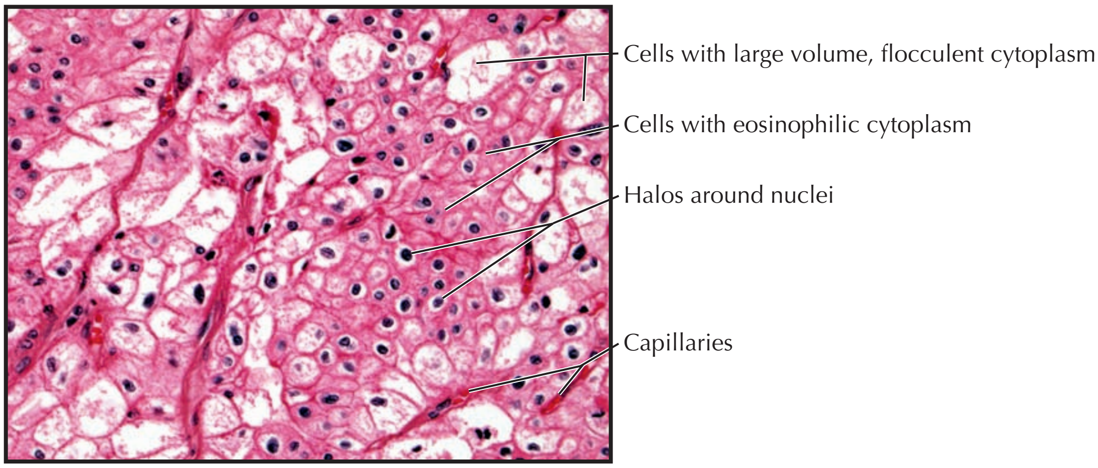
Clear cell carcinoma: H and E Stain


Nests of cells with clear-appearing cytoplasm
Thin, sinusoidal network of capillaries surrounds cell nests

Papillary carcinoma: H and E Stain


Fibrovascular core of large papilla
Small papillae with single layer of carcinoma cells

Chromophobe carcinoma: H and E Stain


Cells with large volume, flocculent cytoplasm
Cells with eosinophilic cytoplasm
Halos around nuclei
Capillaries

Partial nephrectomy is an alternative to radical resection that preserves renal function in the affected kidney. The procedure can be performed using either an open or laparoscopic approach. In recent years, partial nephrectomy has become the standard of care for patients with tumors that are fewer than 4 cm in diameter. This option can be especially important in patients with decreased renal function, a solitary kidney, or a chronic disease that may affect long-term renal function. Careful preoperative and intraoperative imaging is required to adequately identify the tumor's borders and its relationship to major intrarenal vessels and the collecting system.

Ablative procedures, including cryosurgery and radiofrequency ablation, are newer nephron-sparing techniques that have been studied as alternatives to partial nephrectomy. These techniques can be performed from either a percutaneous or laparoscopic approach, and they are associated with shorter recovery times and decreased morbidity. Successful treatment requires adequate intraoperative imaging to ensure optimal placement of the ablation probes, as well as repetitive ablative cycles to ensure complete tumor destruction. Although these procedures are safe and well-tolerated, long-term oncologic data are still relatively limited. The preliminary data, however, demonstrate that recurrence rates may be slightly higher than those following traditional surgery. Nonetheless, ablative techniques are useful options for many patients, including those with contraindications to conventional surgery, those with multiple lesions (in whom partial nephrectomy would be difficult), or those with recurrent disease that requires focal salvage therapy.

In patients who are elderly or are poor candidates for surgery for other reasons, observation is a reasonable alternative. It is generally reserved for patients with small (<3 cm) renal lesions. There is no established standardized protocol for active surveillance; however, most clinicians perform serial imaging every 6 to 12 months to assess for disease progression.

Metastatic Disease. In the past, patients with advanced RCC were not viewed as candidates for surgical resection, given their poor prognosis. Recently, however, advancements in adjuvant therapies have changed the role of surgery in the management of metastatic disease. In patients with good performance status and limited metastatic disease, the goal of surgical resection is to completely remove all affected tissue, including nearby organs and/or abdominal wall muscles. In addition, careful removal of solitary metastases has been shown to improve 5-year survival rates in some patients. Such interventions are cytoreductive and have been shown to improve outcomes if performed before the initiation of adjuvant therapy.

Several biologic agents have been recently developed and studied as treatment for disseminated clear cell RCC. Tyrosine kinase inhibitors, such as sorafenib and sunitinib, have been found to inhibit tumor growth and angiogenesis by blocking the vascular endothelial growth factor receptor (VEGF-R). Meanwhile, bevacizumab is an monoclonal antibody that has also been shown to be effective, and which acts by directly binding circulating VEGF. Additional agents with proven efficacy include mTOR (mammalian target of rapamycin) inhibitors, such as temsirolimus and everolimus. Finally, high-dose interleukin 2 (IL-2) can activate an immune

STAGING SYSTEM AND SITES OF METASTASIS IN RENAL CELL CARCINOMA

	2010 TNM Staging System
T	Tx - Primary tumor cannot be assessed
	T0 - No evidence of primary tumor
	T1 - Tumor 7 cm or less in greatest dimension, limited to the kidney
	T1a - Tumor 4 cm or less
	T1b - Tumor greater than 4 cm but less than or equal to 7 cm
	T2 - Tumor more than 7 cm in greatest dimension, limited to the kidney
	T2a - Tumor greater than 7 cm but less than or equal to 10 cm
	T2b - Tumor greater than 10 cm
	T3 - Tumor extends into major veins or perinephric tissues but not into the ipsilateral suprarenal gland and not beyond the renal fascia
	T3a - Tumor grossly extends into the renal vein or its segmental branches, or tumor invades perirenal and/or renal sinus fat but not beyond the renal fascia
	T3b - Tumor grossly extends into the vena cava below the diaphragm
	T3c - Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
	T4 - Tumor invades beyond the renal fascia (including contiguous extension into the ipsilateral suprarenal gland)
N	NX - Regional lymph nodes cannot be assessed
	N0 - No regional lymph nodes
	N1 - Metastasis in regional lymph node(s)
M	M0 - No distant metastasis
	M1 - Distant metastasis

Stage	
I	T(1)N(0)M(0)
II	T(2)N(0)M(0)
III	T(1/2)N(1)M(0), T(3)N(any)M(0)
IV	T(4)N(any)M(0), T(any)N(any)M(1)

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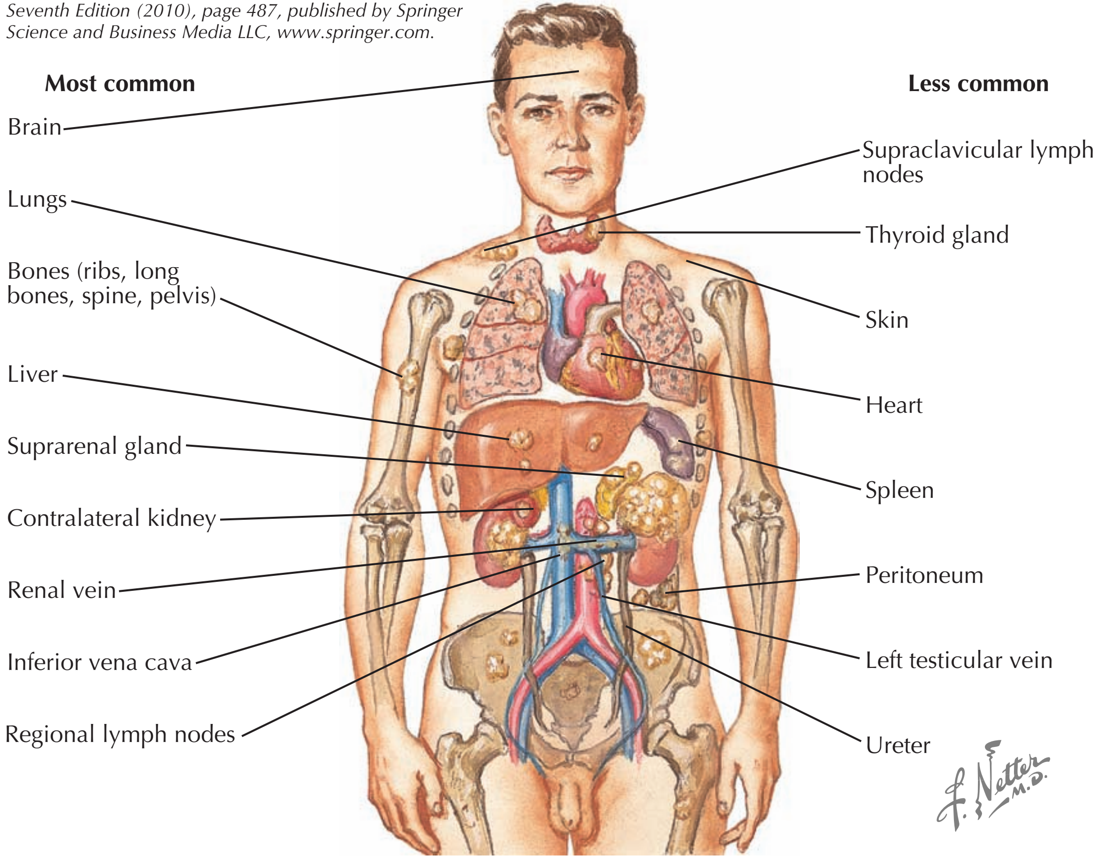
Site of metastasis



RENAL CELL CARCINOMA
(Continued)

response against the tumor, with modest response rates. The effect of these various agents on the growth and overall prognosis of non–clear cell tumors is unclear and remains under active investigation.

PATHOLOGY/GRADING

There are several variants of RCC, which are distinguished based on histomorphology. In addition, there are cytogenetic abnormalities that correlate with the histologic findings. Renal cell carcinoma variants include clear cell (75% to 85%, arising from the proximal tubule), papillary (15%, also arising from the proximal tubule, sometimes termed chromophil), chromophobe (5%, arising from intercalated cells of the cortical collecting duct), unclassified (5%), multilocular clear cell (rare), renal medullary (rare), Xp11 translocation (rare), mucinous tubular, spindle cell (rare), and collecting duct (rare). The histologic features of the most common tumor types are shown in Plate 9-5.

For clear cell carcinomas, the Fuhrman nuclear grading system has prognostic significance and should always be used; it grades these tumors from 1 to 4 based on nucleus size, nucleus shape, and nucleolus appearance. The use of this grading system in non–clear cell carcinomas is less well established.

PROGNOSIS

The prognosis of treated RCC depends on numerous variables, including tumor stage, histopathologic findings, presence or absence of symptoms, laboratory values, and the patient's overall performance status. The tumor stage is the most significant factor, since the 5-year survival of a TNM stage I tumor has been found to be approximately 95%, whereas that of a stage IV tumor is less than 25%. Several scoring systems have been devised to calculate the overall prognosis based on various factors.

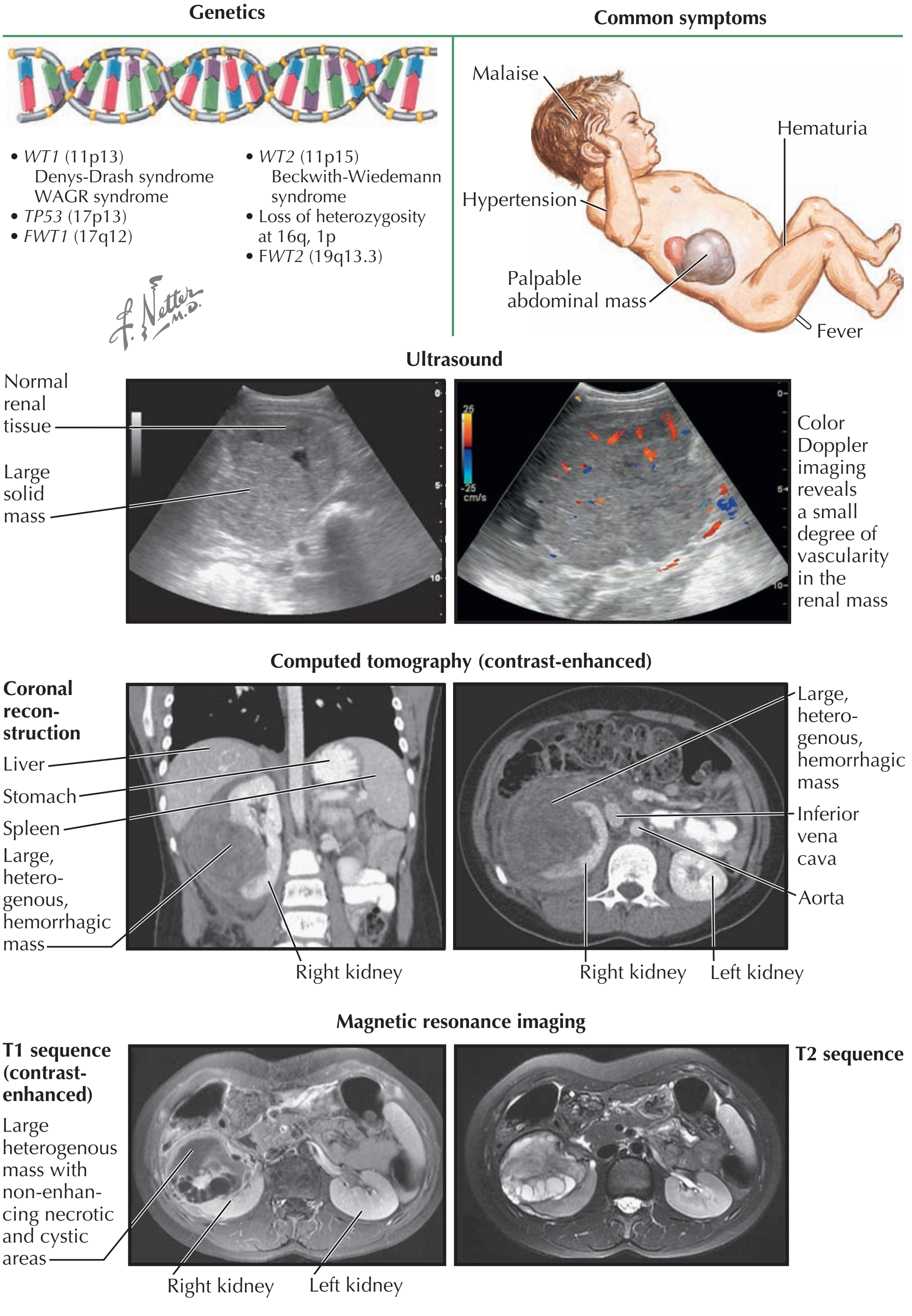
FOLLOW-UP

Although there is no standard recommendation for follow-up of patients who have undergone surgical resection of localized RCC, the frequency and intensity of the protocol are generally dictated by the clinical tumor stage, histopathology, and treatment strategy. Patients are at greatest risk for recurrence in the first 5 years.

Many centers determine their follow-up schedule based on tumor stage. Patients with localized tumors that are less than 7 cm in diameter (T1) are at lowest risk for recurrence. Such patients should undergo annual evaluation that consists of a physical examination, chest radiograph, and laboratory testing of liver and kidney function. Some experts recommend measurement of serum alkaline phosphatase concentrations to monitor for bone metastases; however, the sensitivity and specificity of this laboratory marker are poor.

Patients with masses that are larger than 7 cm or extend into adjacent structures (T2-4) are at higher risk for recurrence and, in addition to the above, should also undergo annual CT scan. Finally, all patients who have undergone a nephron-sparing procedure require an additional CT scan 3 months after the procedure to evaluate the tumor resection site for local disease recurrence.

WILMS TUMOR


Genetics
Common symptoms
• WT1 (11p13)
Denys-Drash syndrome
WAGR syndrome
• TP53 (17p13)
• FWT1 (17q12)
• WT2 (11p15)
Beckwith-Wiedemann syndrome
• Loss of heterozygosity at 16q, 1p
• FWT2 (19q13.3)
Malaise
Hematuria
Hypertension
Palpable abdominal mass
Fever
Ultrasound
Normal renal tissue
Large solid mass
Color Doppler imaging reveals a small degree of vascularity in the renal mass
Computed tomography (contrast-enhanced)
Coronal reconstruction
Liver
Stomach
Spleen
Large, heterogenous, hemorrhagic mass
Right kidney
Large, heterogenous, hemorrhagic mass
Inferior vena cava
Aorta
Right kidney
Left kidney
Magnetic resonance imaging
T1 sequence (contrast-enhanced)
Large heterogenous mass with non-enhancing necrotic and cystic areas
Right kidney
Left kidney
T2 sequence

GENETICS, PRESENTATION, AND RADIOGRAPHIC FINDINGS OF WILMS TUMOR

Wilms tumor, or nephroblastoma, is the most common renal malignancy in children and accounts for 7% of all malignancies in this age group. In the United States, approximately 500 to 600 new cases are diagnosed each year. Most are diagnosed in children between the ages of 2 and 4 years, with more than 80% of cases diagnosed before 5 years of age. Over the past several decades, there has been a substantial improvement in the prognosis of these tumors, with the overall survival rate now 90%.

PATHOGENESIS

Wilms tumors are believed to develop from abnormally persistent nephrogenic rests, which represent undifferentiated metanephric mesenchyme (see Plate 2-1). These rests may be either perilobar, meaning they are confined to the periphery of the kidney and sharply defined, or intralobar, meaning they occur anywhere within the kidney and have indistinct borders. Although nephrogenic rests are seen in up to 1% of newborns, they normally remain dormant, involute, or differentiate. A small minority, however, are believed to give rise to Wilms tumors, as inferred from the fact that 40% of those with unilateral Wilms tumors, and nearly 100% of those with bilateral tumors, have persistent nephrogenic rests.

Abnormalities in several genes have been associated with Wilms tumors. *WT1*, for example, is located on chromosome 11p13 and encodes a zinc finger tumor suppressor important for normal renal and gonadal development. This gene is mutated in about 5% to 15% of Wilms tumors. A subset of patients with *WT1* abnormalities have broader genetic syndromes that feature Wilms tumors as a single component. Denys-Drash syndrome, for example, results from a missense mutation of *WT1* and is associated with Wilms tumors, pseudohermaphroditism, and diffuse renal mesangial sclerosis. Meanwhile, WAGR syndrome results from deletion of *WT1* and is associated with Wilms tumor, aniridia, genitourinary malformations, and mental retardation. The association between Wilms tumor and aniridia reflects the fact that the *PAX6* gene is located adjacent to *WT1* and causes aniridia when mutated.

A second gene, known as *WT2*, is believed to reside within a locus located at chromosome 11p15. This locus contains several genes that are imprinted, meaning that the allele from either the father or the mother is expressed, but not both. Mutations at this locus underpin the Beckwith-Wiedemann syndrome, which features overgrowth (large birth weight, macroglossia, macrosomia, hemihypertrophy, organomegaly), omphalocele, ear pits/creases, and Wilms tumor. Of note, it appears that multiple genes at this locus, rather than a single gene, may be involved in the pathogenesis of Wilms tumor.

In addition to abnormalities in *WT1* and *WT2*, Wilms tumors have also been associated with loss of heterozygosity at 16q and 1p, as well as with mutations in p53 (encoded on 17p13).

Most of the mutations underlying Wilms tumors are believed to arise either in the germ line or in the tumor tissue alone. Thus despite these numerous genetic associations, only a very small minority of patients who develop Wilms tumors have a positive family history. In such patients, abnormalities are not at 11p but rather at 17q12-21 (*FWT1)* and 19q13.3-13.4 (*FWT2)*.

PRESENTATION AND DIAGNOSIS

In a vast majority of children with Wilms tumor, the presenting symptom is a palpable abdominal mass, which may be associated with abdominal pain, hematuria (from extension into the collecting system or ureter), and/or hypertension (from increased renin secretion). Other nonspecific symptoms, which may occur in some cases, include fever, malaise, and weight loss.

Ultrasound should be the initial study to assess for the presence of a renal mass and, if one is seen, to determine with color Doppler imaging if there is extension into the inferior vena cava. If a renal tumor is seen, or if the kidney cannot be adequately visualized, CT or MRI should be performed.

WILMS TUMOR *(Continued)*

Other pediatric intraabdominal malignancies or benign lesions that should be considered include other renal tumors, neuroblastoma, teratoma, lipoma, hamartoma, and lymphoma. In most cases, complete surgical excision and histopathologic examination of the tumor is necessary to establish the definitive diagnosis.

TREATMENT

According to the most common protocols, patients are treated with primary surgical excision of the tumor. If there is a unilateral tumor, nephrectomy is performed along with sampling of hilar and ipsilateral paraaortic or caval lymph nodes. If there are bilateral tumors, as in 5% of cases, a biopsy should be performed first to confirm the diagnosis, then neoadjuvant chemotherapy should be administered to reduce the tumor burden. Once neoadjuvant therapy is complete, renal-sparing surgery (such as partial nephrectomy) should be performed to preserve as much renal function as possible.

After surgery, subsequent treatment is based on the stage and histopathologic tumor subtype. According to the National Wilms Tumor Study guidelines, stage I tumors are confined to the kidney and can be completely removed with surgery. Stage II tumors penetrate the capsule and may invade adjacent vessels but can nonetheless be completely removed with surgery. Stage III tumors have positive margins or nonhematogenous intraabdominal spread (i.e., lymph node involvement, tumor spillage, peritoneal involvement) that remains after surgery. Stage IV tumors have hematogenous metastases to distant sites, such as the lung, liver, bone, or brain. Stage V tumors are bilateral. All of these stages receive an "A" suffix if surgical histopathology reveals anaplastic features.

For patients with stage I or II tumors, treatment consists of nephrectomy and adjuvant chemotherapy. A subgroup of patients (<2 years of age and less than 550 g of body weight) with stage I tumors may only require observation after surgery because their prognosis seems extremely favorable. For patients with stage III or IV tumors, treatment consists of nephrectomy followed by adjuvant chemotherapy and radiotherapy. For patients with stage V tumors, neoadjuvant treatment is offered, as described previously, followed by a reassessment of the tumor burden of each kidney and nephron-sparing surgery whenever possible.

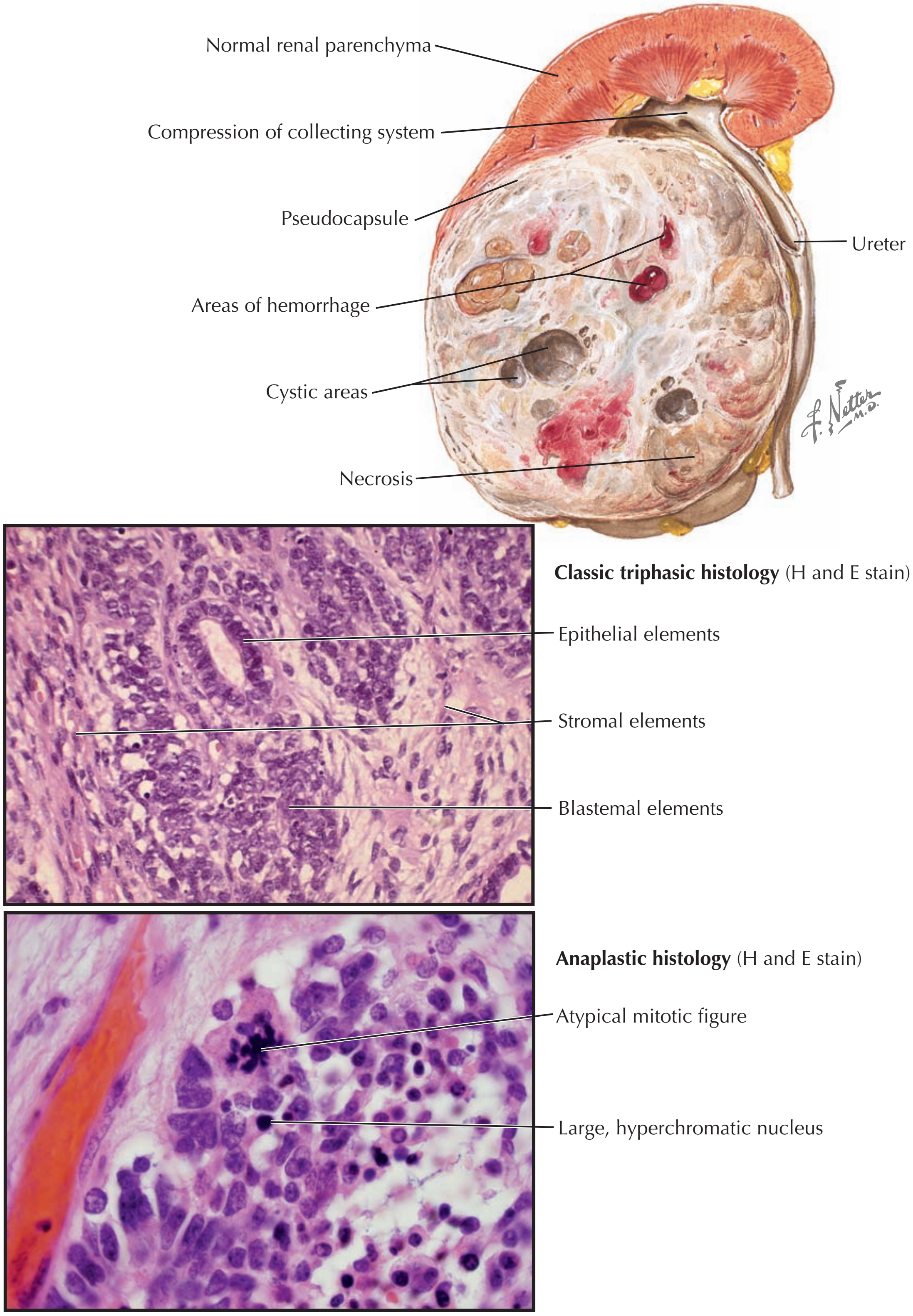
The recommended chemotherapy regimens include various combinations of vincristine, dactinomycin, doxorubicin, and cyclophosphamide, with the specific regimens varying based on tumor stage, histopathologic findings, and mutation profile (e.g., presence or absence of loss of heterozygosity at 1p and 16q).

The histopathologic findings are important predictors of the response to chemotherapy. Wilms tumors classically contain blastemal, epithelial, and stromal components. The blastemal cells are dense, undifferentiated, and haphazardly arranged in sheets. The epithelial cells are columnar or cuboidal and line tubules. The stromal cells have a variable appearance, ranging from nondescript spindle cells to more differentiated cells, such as those characteristic of muscle, fat, or bone. All three components may be present, or one or more may be absent. Tumors with predominantly epithelial and stromal components are generally less aggressive. Tumors with predominantly blastemal features are more aggressive but still respond to chemotherapy in most cases. Tumors with poorly differentiated, anaplastic cells (which contain multipolar mitotic figures and enlarged, hyperchromatic nuclei) respond poorly to chemotherapy and radiotherapy.

FOLLOW-UP

The recommended schedule for follow-up examinations and testing after treatment depends on the initial stage of the cancer and treatment type. Follow-up visits should consist of physical examinations and imaging tests (chest radiograph, abdominal ultrasound) to rule out tumor recurrence and to assess for possible side effects of chemotherapy or radiotherapy. Blood and urine tests should also be performed during every follow-up visit to evaluate remaining renal function. The frequency of follow-up visits can decrease over time if no abnormal or concerning findings are noted.

GROSS APPEARANCE AND HISTOPATHOLOGIC FINDINGS OF WILMS TUMOR



Tumors of the Renal Pelvis and Ureter

A vast majority of the tumors that originate in the renal pelvis and ureter develop from urothelial cells, which line the renal calices, ureters, and bladder. Urothelial carcinomas (also known as transitional cell carcinomas) of the upper urinary tract represent less than 10% of all renal tumors and only 5% of all urothelial carcinomas.

Approximately 5% of ureteral tumors are in the proximal ureter, 25% are in the midureter, and 70% are in the distal ureter. Moreover, patients with an upper tract tumor are much more likely to develop a bladder tumor than vice versa. The reason for this apparent downstream effect is not clear; however, it has been hypothesized to reflect downstream seeding or longer exposure of bladder urothelium to carcinogens.

RISK FACTORS

Upper tract urothelial carcinomas tumors occur on average in the seventh decade. Men and Caucasians are twice as likely to develop these tumors as women and African Americans.

Several genetic and environmental risk factors are known. Many are shared with urothelial carcinoma of the bladder, including cigarette smoking, aromatic amine (e.g., aniline) exposure, cyclophosphamide exposure, and mutations in certain genes (e.g., *TP53* and *RB*).

Other factors, however, appear to increase the risk of upper tract carcinomas in particular. Phenacetin abuse, for example, has been associated not only with analgesic nephropathy (see Plate 4-30) but also with upper tract urothelial carcinomas. In addition, the interstitial nephropathy known as Balkan nephropathy (seen primarily in populations near the Danube River and its tributaries) increases the risk of upper tract urothelial carcinomas. Finally, hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome) is an autosomal dominant condition characterized by altered DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*) and increased risk of cancer in the stomach, small intestine, colon, liver, endometrium, ovary, and upper urinary tract (urothelial type).

PRESENTATION AND DIAGNOSIS

The major presenting symptom of an upper tract urothelial carcinoma is gross or microscopic hematuria. If there is obstruction of the ureter, dull flank pain may also occur.

Patients suspected of having upper tract malignancies should be evaluated using contrast-enhanced CT, which may reveal a visible mass or filling defect on delayed urographic phase. If there is a chronic obstruction to urine outflow, dilation of the renal pelvis and ureter may be seen, depending on the level of the mass.

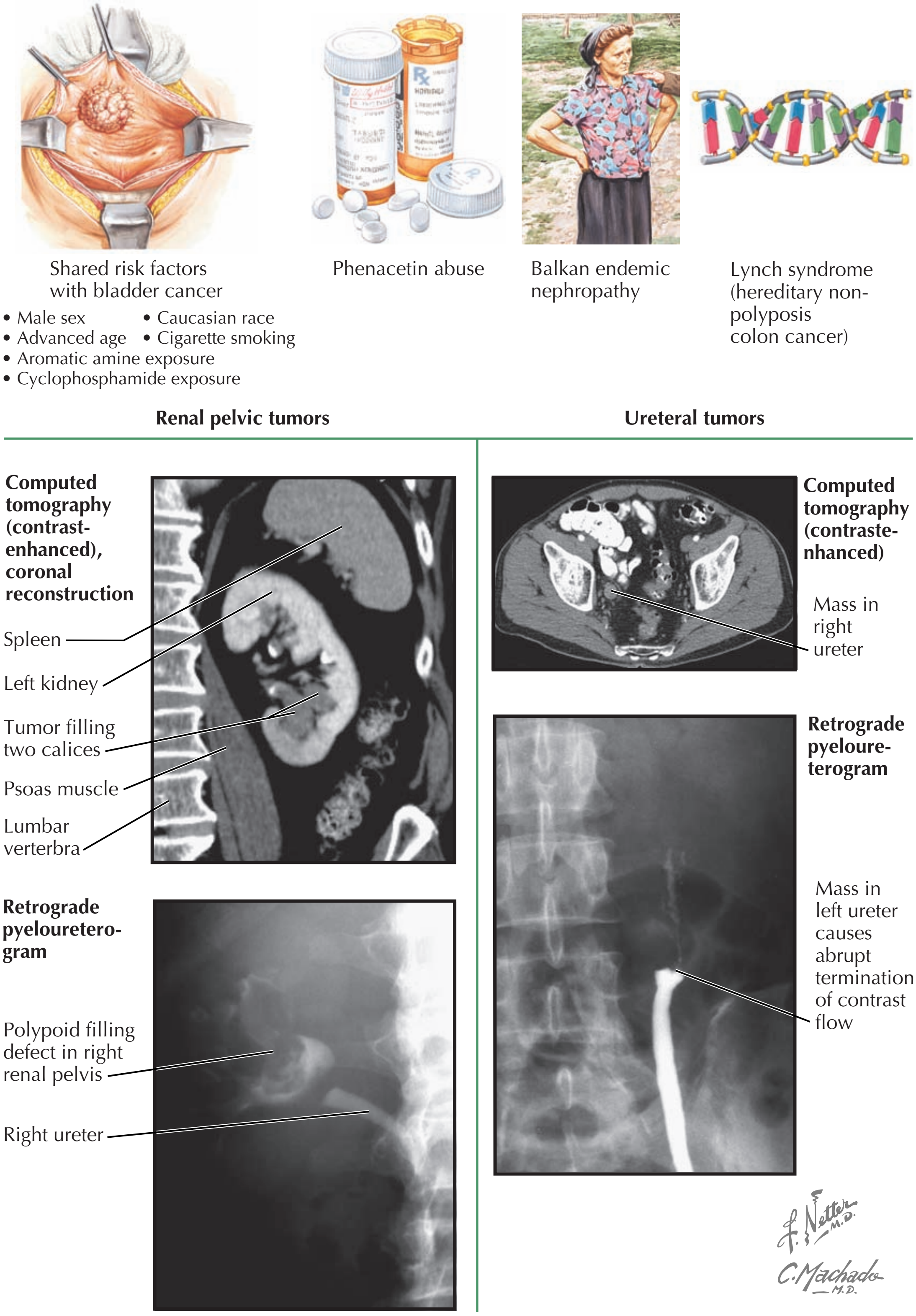
The presence of regional extension or metastases may also be assessed using various radiographic modalities. Urothelial carcinomas of the upper tract, like those of the bladder, may metastasize to lymph nodes, liver, lung, and bone. CT can be used to assess for the presence of abdominal or pelvic metastases. Chest radiograph is often adequate to screen for the presence of lung metastases. A bone scan may be performed to evaluate for bone metastases in the setting of suggestive symptoms or elevated serum alkaline phosphatase concentration.

Once the presence of an upper tract tumor has been established, cystoureteroscopy should be performed to examine the entire urine collecting system. A retrograde pyeloureterogram performed during this procedure often reveals a filling defect in the area of the tumor. All abnormal-appearing areas should undergo directed biopsy. The histopathologic findings of upper tract urothelial carcinomas are similar to those of the lower tract and are classified in a similar manner. Once the tumor has been radiographically and pathologically characterized, initial staging can be performed according to TNM criteria.

TREATMENT

Surgery is the therapy for localized disease. The optimal approach depends on characteristics of both the patient and tumor.

Risk Factors and Radiographic Appearance of Tumors of the Renal Pelvis and Ureter


Shared risk factors with bladder cancer
• Male sex
• Caucasian race
• Advanced age
• Cigarette smoking
• Aromatic amine exposure
• Cyclophosphamide exposure
Phenacetin abuse
Balkan endemic nephropathy
Lynch syndrome (hereditary non-polyposis colon cancer)
Renal pelvic tumors
Ureteral tumors
Computed tomography (contrast-enhanced), coronal reconstruction
Spleen
Left kidney
Tumor filling two calices
Psoas muscle
Lumbar verterbra
Retrograde pyeloureterogram
Polypoid filling defect in right renal pelvis
Right ureter
Computed tomography (contraste-nhanced)
Mass in right ureter
Retrograde pyeloureterogram
Mass in left ureter causes abrupt termination of contrast flow
F. Netter M.D.
C. Machado M.D.

Tumors of the Renal Pelvis and Ureter *(Continued)*

For a patient with a normally functioning contralateral kidney, the gold-standard treatment is radical nephroureterectomy, in which the entire kidney and ureter on the affected side are removed, along with a cuff of normal-appearing bladder. Removal of the entire urothelial tract is essential because there is a high risk of recurrent disease if a ureteral stump is left behind.

Radical nephroureterectomy can be performed from either an open or laparoscopic approach. Regional lymphadenectomy is usually performed simultaneously. For proximal tumors, the ipsilateral renal hilar, para-aortic, and paracaval nodes are removed; for distal tumors, the ipsilateral pelvic lymph node chains are removed. The main benefit to lymph node dissection is more accurate staging of the tumor, which may provide prognostic information and determine eligibility for trials of adjuvant chemotherapy. There is no evidence, however, that there is any survival benefit to lymphadenectomy itself because patients with node-positive disease often have distant metastasis at the time of node dissection.

For a patient with a small, localized, low-grade tumor, or with a relative contraindication to nephroureterectomy (solitary functional kidney, bilateral upper tract tumors, chronic kidney disease, severe comorbid illness), a nephron-sparing approach may be used instead. In most cases, the tumor is accessed using retrograde ureteroscopy. After initial debulking with a basket, forceps, or other device, the tumor is ablated using a laser or monopolar electrocautery. If the tumor cannot be adequately treated from a retrograde approach, a percutaneous anterograde approach using a nephroscope may be undertaken.

For a patient with a tumor confined to the distal ureter, selective distal ureterectomy with ureter reimplantation may be an option if there is a relative contraindication to nephroureterectomy (see previous list) or the tumor is small and low grade.

Systemic chemotherapy may be administered either before surgery (neoadjuvant) or after extirpation (adjuvant). Because urothelial carcinomas of the upper tract are relatively rare, however, there are no randomized controlled trials that substantiate the benefit of chemotherapy in patients with advanced or metastatic lesions. Nonetheless, in patients with known metastasis, chemotherapy regimens are typically employed and are similar to those used for urothelial carcinomas of the bladder (i.e., cisplatin-based). In general, however, patients with metastatic upper tract tumors have a poor outcome no matter the treatment strategy.

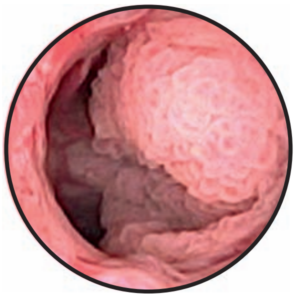
PROGNOSIS

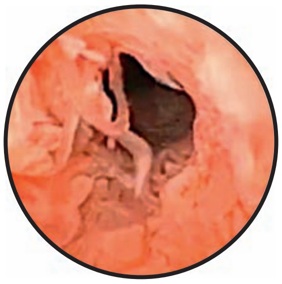
Tumor stage and grade are critical factors when determining an individual patient's prognosis. Following radical nephroureterectomy, one series noted 5-year disease-specific survival rates of 100% with Ta/Tis disease, 92% with T1 disease, 73% for T2 disease, 40% for T3 disease, and 0% for T4 disease. Another series noted 5-year disease-specific survival rates of 94% with Ta/Tis disease, 91% with T1 disease, 75% with T2 disease, 54% with T3 disease, and 12% with T4 disease. In addition, this series found 5-year disease-specific survival rates to be 89% with low-grade disease and 63% with high-grade disease. The type of surgical intervention also affects outcomes because a higher risk of recurrence has been observed among those treated using an endourologic approach.

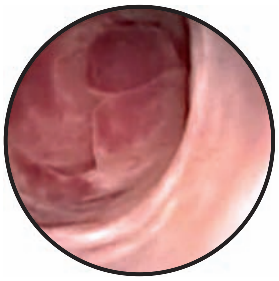
FOLLOW-UP

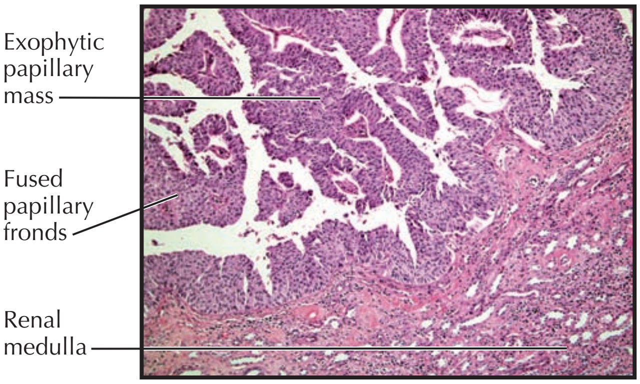
A significant subset of the patients treated for urothelial carcinoma of the upper tract will subsequently develop bladder cancer. Thus it is essential to perform surveillance of all patients with regular examination, cytoscopy, urine cytology, and CT of the abdomen and pelvis for several years after initial treatment. In patients who have undergone nephron-sparing treatment, surveillance ureteroscopy is often indicated as well.

Appearance (Ureteroscopic, Gross, and Microscopic) and Staging of Tumors of the Renal Pelvis and Ureter

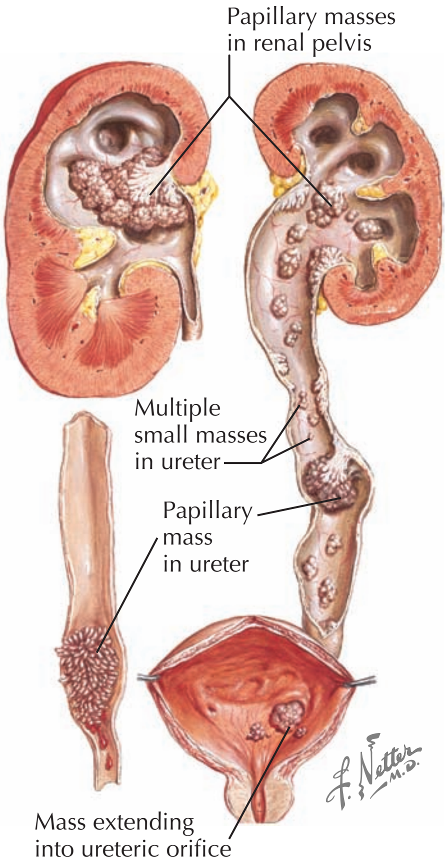

Cauliflower-like papillary mass of the renal pelvis


Papillary mass of the ureter with fronds projecting into lumen


Solid-appearing mass of the ureter



Non-invasive low-grade papillary urothelial carcinoma of the renal pelvis (H and E stain)


Papillary masses in renal pelvis
Multiple small masses in ureter
Papillary mass in ureter
Mass extending into ureteric orifice
F. Netter M.D.

2010 TNM Staging System	
T	Tx - Primary tumor cannot be assessed
	T0 - No evidence of primary tumor
	Ta - Noninvasive papillary carcinoma
	Tis - Carcinoma in situ
	T1 - Tumor invades subepithelial connective tissue
	T2 - Tumor invades muscularis propria
	T3 - *In renal pelvis*: tumor invades into peripelvic fat or the renal parenchyma *In ureter*: tumor invades periureteric fat
	T4 - Tumor involves adjacent organs or through the kidney into the perinephric fat
N	NX - Regional lymph nodes cannot be assessed
	N0 - No regional lymph nodes metastasis
	N1 - Metastasis in a single lymph node 2 cm or less in greatest dimension
	N2 - Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
	N3 - Metastasis in a lymph node more than 5 cm in greatest dimension
M	M0 - No distant metastasis
	M1 - Distant metastasis

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Stage	
0A	T(a)N(0)M(0)
0is	T(is)N(0)M(0)
I	T(1)N(0)M(0)
II	T(2)N(0)M(0)
III	T(3)N(0)M(0)
IV	T(4)N(0)M(0) T(any)N(1–3)M(0) T(any)N(any)M(1)

TUMORS OF THE BLADDER

More than 90% of bladder cancers arise from the mucosa and are known as urothelial (transitional cell) carcinomas. These tumors are the main focus of this section. Less common tumors include squamous cell carcinomas (≤5% in the United States, but most common worldwide), adenocarcinomas (2%), small cell carcinomas, and nonepithelial tumors. Metastatic tumors from other primary sites—including the prostate, ovary, uterus, colon, rectum, and lung—have also been described.

EPIDEMIOLOGY AND RISK FACTORS

In the United States, bladder cancer is the fourth most common malignancy among men, affecting an estimated 52,000 in the United States in 2010. It is three times more common in men than in women, and it is twice as common in Caucasian than in African American men. Like upper tract cancer, bladder cancer is generally a disease of older patients, with an average age at diagnosis of approximately 70 years.

The major risk factor for urothelial carcinoma of the bladder is cigarette smoking. Inherited differences in the metabolism of cigarette carcinogens appear to modulate this risk; for example, slower acetylators of N-acetyltransferase (NAT) are at increased risk. Another significant risk factor is occupational exposure to aromatic amines, such as 2-naphthylamine, 4-aminobiphenyl, and 4,4′-diaminobiphenyl (benzidine). These exposures are most significant among textile workers from the aniline dye and rubber industries. Other risk factors include cyclophosphamide exposure and prior pelvic radiation.

These carcinogens appear to induce genetic abnormalities that contribute to the development of urothelial carcinomas, including mutations of the p53 tumor suppressor gene (*TP53*, on chromosome 17p) and retinoblastoma gene (*RB*, on chromosome 13q). Since these mutations are generally acquired, a prior family history of bladder cancer appears to cause only a slight increase in risk.

PRESENTATION AND DIAGNOSIS

Approximately 85% of patients with bladder cancer have painless gross hematuria. In adults, this symptom should be considered highly suspicious for cancer unless there is compelling evidence that the blood is of glomerular origin (i.e., large numbers of red blood cell casts or dysmorphic red blood cells are seen). 20% to 30% of patients also experience bladder irritability, urinary frequency, urgency, and/or dysuria. More advanced bladder cancers may rarely be associated with flank pain from ureteral obstruction or lower extremity edema from lymphatic or venous obstruction. On physical examination, a bimanual examination (rectoabdominal in men, vaginoabdominal in women) may reveal a palpable mass in advanced cases; however, most examinations are unremarkable.

Once bladder cancer is suspected, radiographic imaging, urine cytology, and cystoscopy are required for further evaluation.

On high-quality axial imaging using CT or MRI, tumors may be seen as enhancing masses that produce filling defects in the bladder lumen. Because urothelial tumors arising in the upper urinary tract may seed the bladder, it is also important to perform upper tract imaging. MRI of the bladder may be used to estimate the depth of invasion into the muscularis propria (detrusor muscle) and perivesical structures.

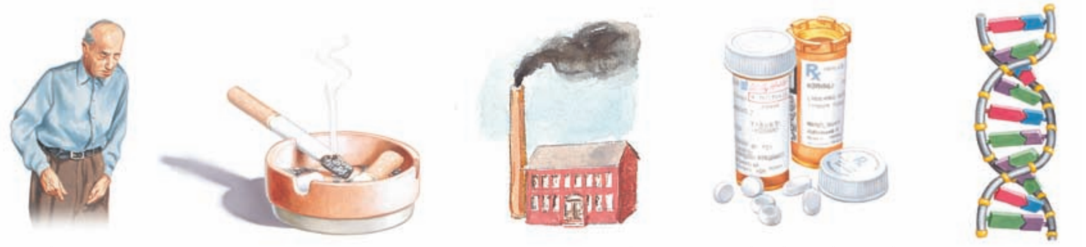
Metastases most frequently occur in lymph nodes, liver, lung, bone, and adrenal glands. CT or MRI of the abdomen and pelvis is used to assess for nodal, liver, and adrenal metastases. Chest radiographs are typically performed to screen for lung metastases, given the high rate of false positives on CT scan. Radionuclide bone scans may be used to determine the presence of skeletal metastases in patients with suggestive symptoms or elevated serum alkaline phosphatase concentrations.

Urine cytology detects malignant urothelial cells in voided urine specimens or bladder washings. Current techniques are highly specific but only moderately sensitive, with the highest likelihood of a positive result in a patient with an advanced tumor.

Cystoscopy provides direct visual examination of the bladder mucosa, and it is the gold standard for

RISK FACTORS, SYMPTOMS, AND PHYSICAL EXAMINATION FOR TUMORS OF THE BLADDER

Risk factors



Male sex
Advanced age

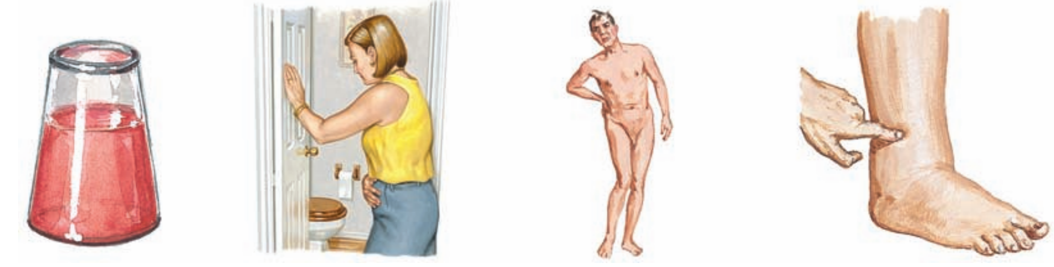
Cigarette smoking

Occupational exposure to aromatic amines

Cyclophosphamide exposure

Genetics *(TP53, RB)*

Symptoms



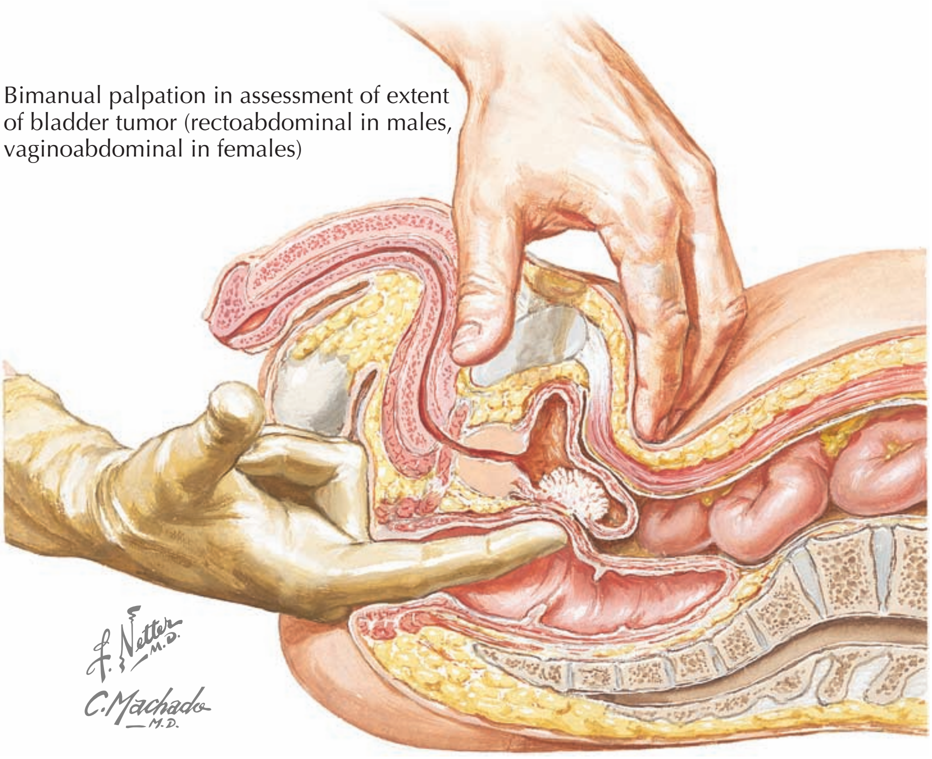
Hematuria, either gross or microscopic (predominant symptom)

Urinary frequency
Urinary urgency
Dysuria

Flank pain (rare, suggests an advanced mass)

Lower extremity edema (rare, suggests an advanced mass)

Bimanual examination



Bimanual palpation in assessment of extent of bladder tumor (rectoabdominal in males, vaginoabdominal in females)

TUMORS OF THE BLADDER

(Continued)

diagnosis. Many grossly visible tumors can be resected during this initial evaluation (see Plate 10-39). Any abnormal-appearing or erythematous areas of mucosa should undergo directed biopsy for histopathologic examination. Random biopsies of normal-appearing areas may also be indicated, especially if urine cytology is positive but no tumor is grossly visible. Additional biopsy sites may include areas adjacent to a tumor, from the opposite bladder wall, dome, trigone, and prostatic urethra. It is essential to obtain deep tissue samples with adequate representation of the bladder wall to perform accurate staging.

PATHOLOGY/GRADING

Urothelial tumors differ from normal urothelium in architectural growth and cytologic features. They are graded according to World Health Organization/International Society of Urological Pathology Consensus criteria, which were developed in 1998 and revised in 2004.

Noninvasive. Noninvasive tumors, which do not cross the basement membrane into the lamina propria, are classified as flat or papillary.

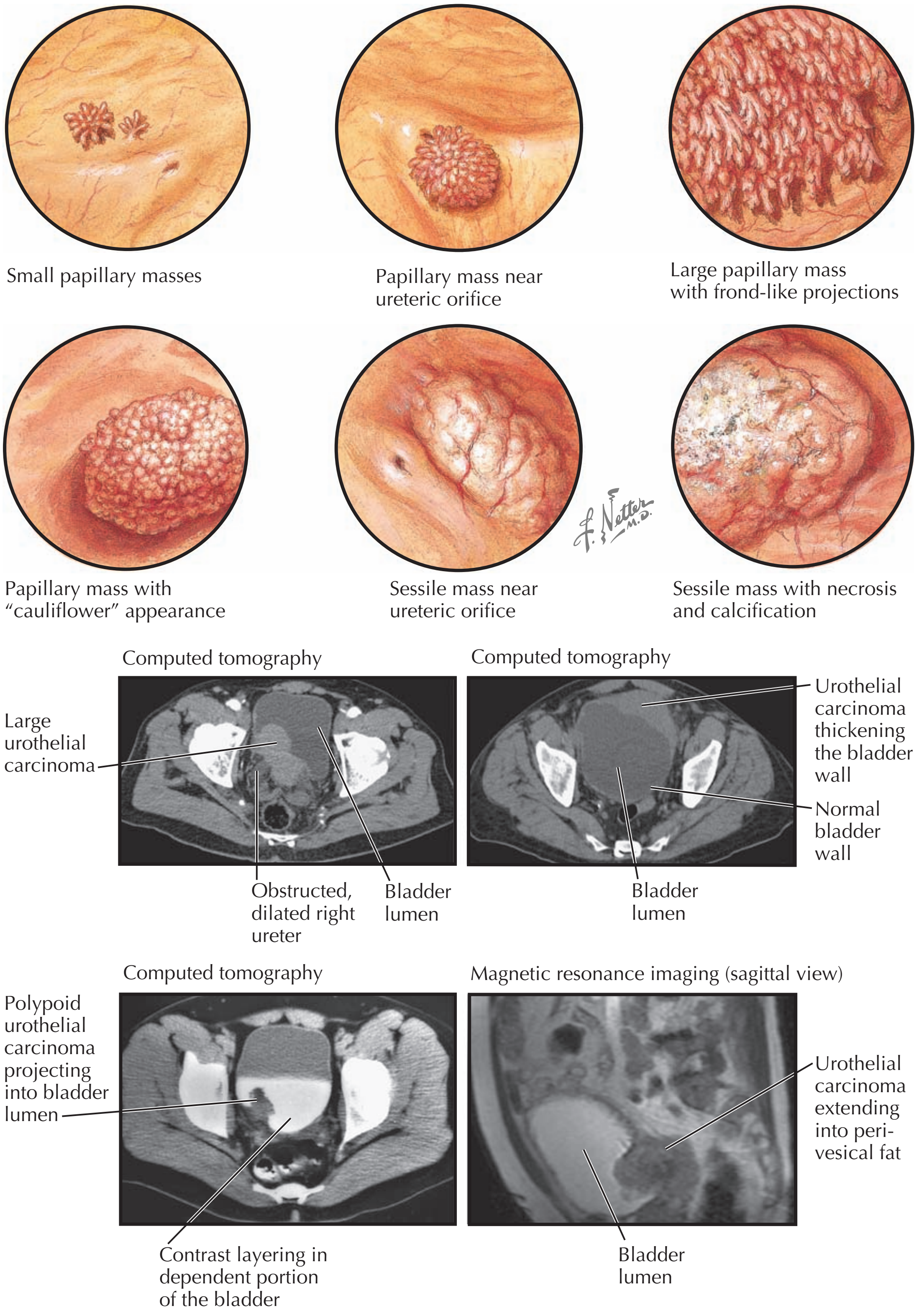
Flat lesions include reactive atypia, atypia of unknown significance, dysplasia (low-grade intraurothelial neoplasia), or carcinoma in situ (high-grade intraurothelial neoplasia). Carcinoma in situ (CIS) is a precursor of invasive high-grade cancer. It is confined to the epithelial layer, and characteristic features include nuclear enlargement, hyperchromasia, crowding, and atypia.

Papillary tumors include papillomas, papillary urothelial neoplasms of low malignant potential (PUNLMP), and low- or high-grade papillary urothelial carcinomas (LGPUC and HGPUC). Papillomas are benign lesions. PUNLMP have a low recurrence risk and only a rare association with carcinoma. The major differentiating feature between papilloma and PUNLMP is the presence of thicker urothelium and enlarged nuclei in the latter.

LGPUC and HGPUC are malignant lesions. These feature proliferation of malignant urothelial cells along exophytic fibrovascular cores, as well as papillary frond fusion and branching complexity. LGPUC features neoplastic cells that vary in polarity and possess cytologic atypia and some mitotic figures. HGPUC, in turn, features marked nuclear pleomorphism, a high nuclear-cytoplasmic ratio, and frequent mitotic figures. HGPUC has a higher rate of progression than LGPUC, as well as a higher probability of invasive disease and concomitant CIS at diagnosis. Heterogeneous tumors are graded based on the highest grade represented.

Invasive. Invasive carcinomas (crossing the basement membrane into the lamina propria, possibly into the muscularis propria) are also differentiated as low or high grade. Low-grade carcinomas have an ordered appearance but with nuclear variation and enlargement compared with normal urothelium. High-grade carcinomas have a disordered appearance with marked nuclear pleomorphism. The vast majority of invasive urothelial carcinomas are high grade.

CYSTOSCOPIC AND RADIOGRAPHIC APPEARANCE OF TUMORS OF THE BLADDER


Small papillary masses

Papillary mass near ureteric orifice

Large papillary mass with frond-like projections

Papillary mass with "cauliflower" appearance

Sessile mass near ureteric orifice

Sessile mass with necrosis and calcification

Computed tomography

Computed tomography

Computed tomography

Magnetic resonance imaging (sagittal view)

Large urothelial carcinoma
Obstructed, dilated right ureter
Bladder lumen
Urothelial carcinoma thickening the bladder wall
Normal bladder wall
Bladder lumen
Polypoid urothelial carcinoma projecting into bladder lumen
Contrast layering in dependent portion of the bladder
Urothelial carcinoma extending into perivesical fat
Bladder lumen

Although grading can only be performed by histologic examination of tissue, cystoscopic findings may have some predictive value. For example, a histologically benign papilloma or a low-grade papillary tumor usually appears as a fine villous structure attached to the bladder by a thin pedicle. By contrast, a higher-grade papillary carcinoma is usually denser with a cauliflower appearance and a thicker pedicle. CIS is a flat lesion. Deeper invasion may be indicated by a nodular or sessile appearance, sometimes with necrosis. If there is tumor obstruction of the ureteric orifice, there is likely deeper infiltration.

STAGING

Staging of a bladder tumor, performed according to the 2010 TNM classification system, measures the precise extent of the tumor's spread both within and beyond the bladder wall. It relies on information from biopsy and imaging.

Tumors of the Bladder

(Continued)

The staging of a bladder tumor offers important prognostic information. Prognosis also correlates with tumor size, multiplicity, papillary versus sessile configuration, presence of lymphovascular invasion, and status of the remaining urothelium.

TREATMENT

The specific treatment plan must be based on the tumor stage and the clinical condition of the patient. A key factor is whether the tumor invades the muscularis propria, and if so, whether aggressive treatment is likely to be curative.

Low-risk, noninvasive tumors (i.e., low-grade Ta) are typically treated with transurethral resection (TURBT, see Plate 10-39), generally performed at the time of initial cystoscopic evaluation, as well as intravesical chemotherapy (i.e., mitomycin C). The patient, however, must undergo routine cystoscopic surveillance because recurrence is common.

High-risk, noninvasive tumors (high-grade Ta, Tis, or T1) are typically treated with transurethral resection and intravesical immunotherapy with bacillus Calmette-Guérin (BCG), an attenuated mycobacterium that induces a local, antitumor immune response that decreases recurrence and progression rates. Patients failing this treatment may be offered second-line intravesical therapy (BCG-interferon or alternative chemotherapy), but radical cystectomy should be strongly considered.

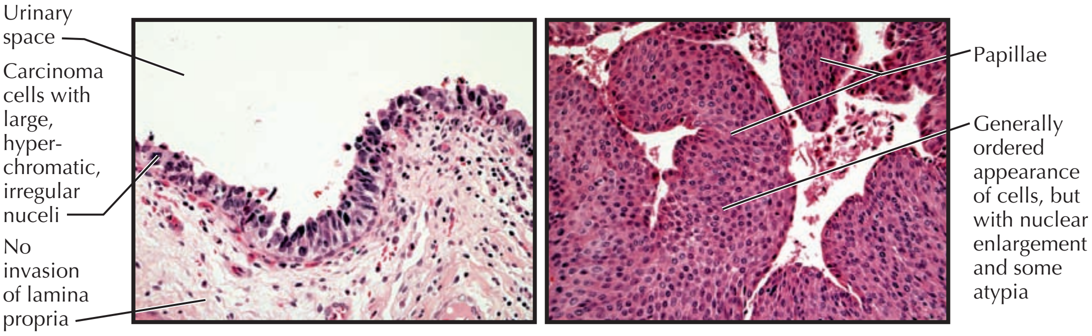
Local muscularis propria-invasive tumors are aggressively treated, typically using a combination of neoadjuvant, cisplatin-based chemotherapy and radical cystectomy with urinary diversion. Randomized trials have shown that a multiagent chemotherapeutic regimen followed by radical cystectomy is more likely to eliminate cancer than radical cystectomy alone. The relative reduction of 25% to 40% in all-cause and cancer-specific mortality is associated with an improvement of median overall survival by 2.5 years. Nonrandomized clinical trials have demonstrated the efficacy of neoadjuvant chemotherapy and external radiation therapy in select patients. Adjuvant systemic chemotherapy may provide a survival advantage for locoregional disease with pelvic lymph node involvement, with up to 9% improvement in survival at 3 years.

Unresectable or metastatic bladder cancer is treated with systemic, cisplatin-based chemotherapy alone.

Histopathologic Findings and Staging System of Tumors of the Bladder

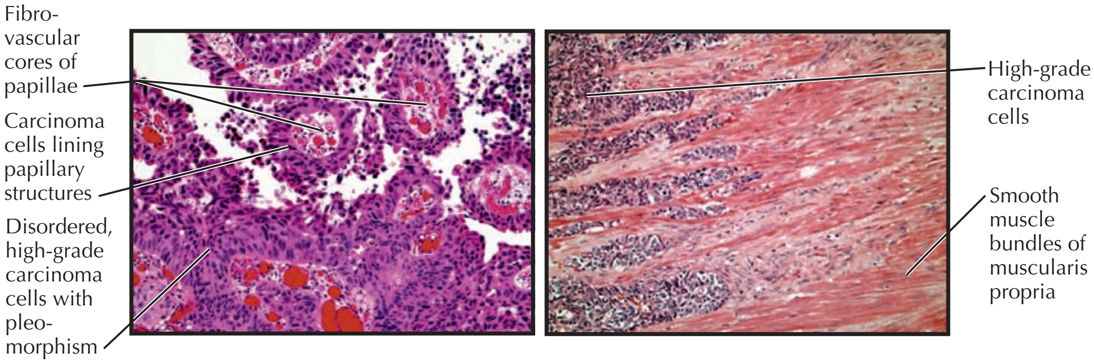
Urothelial carcinoma in situ (H and E stain)

Noninvasive low-grade papillary urothelial carcinoma (H and E stain)


Urinary space
Carcinoma cells with large, hyper-chromatic, irregular nuceli
No invasion of lamina propria
Papillae
Generally ordered appearance of cells, but with nuclear enlargement and some atypia

Noninvasive high-grade papillary urothelial carcinoma (H and E stain)

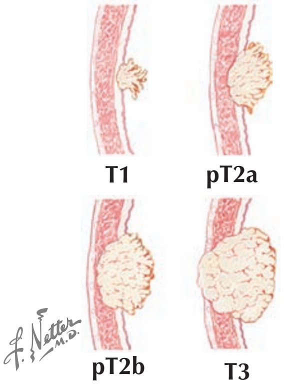
Muscularis propria invasive, high-grade carcinoma (H and E stain)


Fibro-vascular cores of papillae
Carcinoma cells lining papillary structures
Disordered, high-grade carcinoma cells with pleo-morphism
High-grade carcinoma cells
Smooth muscle bundles of muscularis propria

2010 TNM Staging System

T	Tx - Primary tumor cannot be assessed
	T0 - No evidence of primary tumor
	Ta - Noninvasive papillary carcinoma
	Tis - Carcinoma in situ
	T1 - Tumor invades subepithelial connective tissue
	T2 - Tumor invades muscularis propria
	pT2a - Tumor invades superficial muscularis propria (inner half)
	pT2b - Tumor invades deep muscularis propria (outer half)
	T3 - Tumor invades perivesical tissue
	pT3a - Microscopically
	pT3b - Macroscopically
	T4 - Tumor invades any of the following:
	T4a - Prostatic stroma, uterus, vagina
	T4b - Pelvic wall, abdominal wall
N	NX - Lymph nodes cannot be assessed
	N0 - No lymph nodes metastasis
	N1 - Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
	N2 - Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes)
	N3 - Lymph node metastasis to the common iliac lymph nodes
M	M0 - No distant metastasis
	M1 - Distant metastasis

Stage	
0A	T(a)N(0)M(0)
0is	T(is)N(0)M(0)
I	T(1)N(0)M(0)
II	T(2a/b)N(0)M(0)
III	T(3a/b or 4a) N(0)M(0)
IV	T(4b)N(0)M(0) T(any)N(1–3)M(0) T(any)N(any)M(1)



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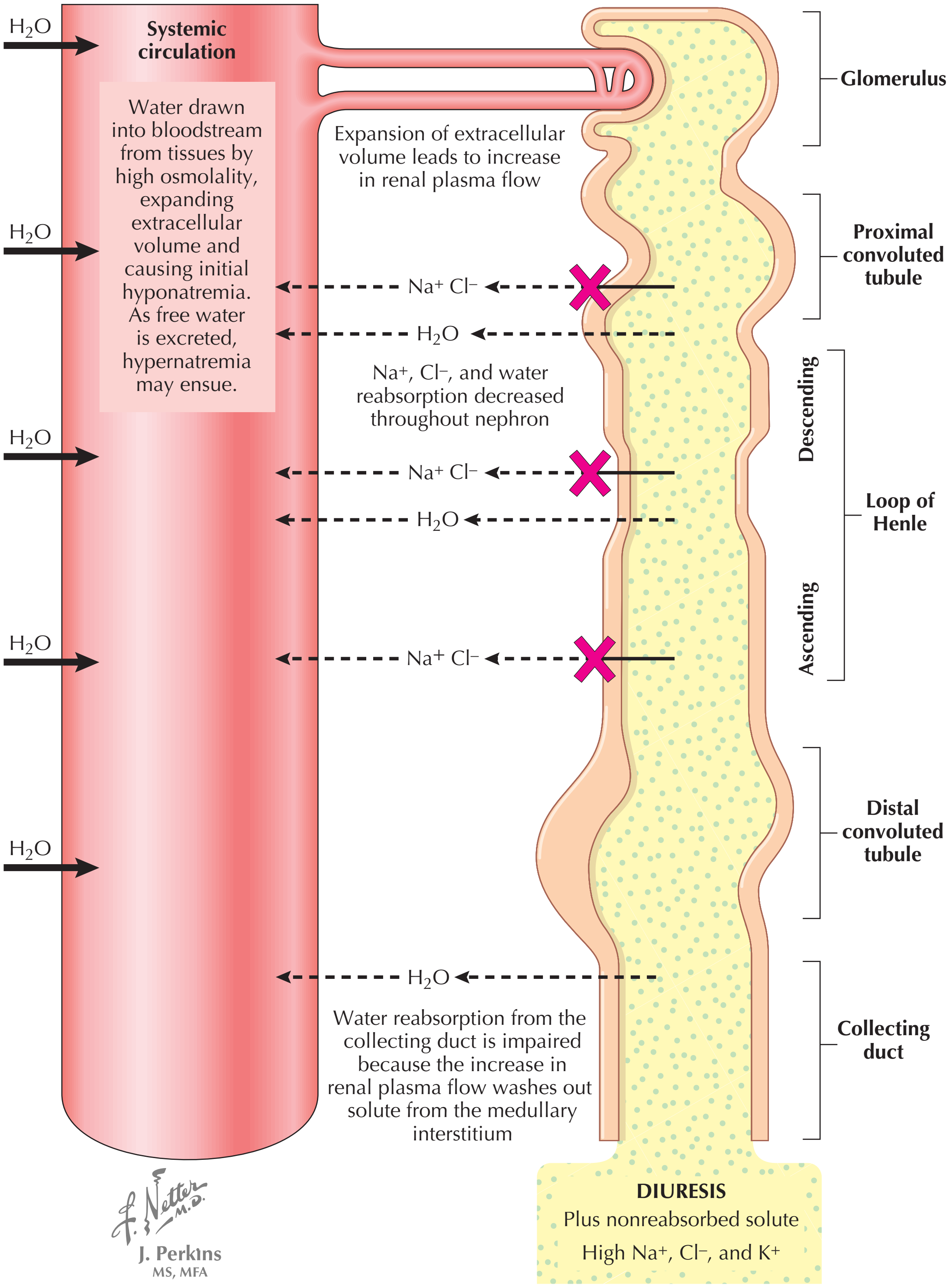
FOLLOW-UP

Patients with noninvasive bladder cancers that are treated with TURBT, either with or without intravesical therapy, should undergo routine follow-up with flexible cystoscopy and urine cytology every 3 months for 1 to 3 years. The frequency can then be reduced to every 6 months for an additional 2 to 3 years, and then annually, as long as there has been no recurrence. Disease status at the initial 3-month treatment is important in predicting tumor behavior in the future. In addition to these measures, contrast-enhanced CT or retrograde pyelogram should be performed at least every 1 to 2 years.

Patients with invasive disease treated with cystectomy should undergo lifelong follow-up, with a chest radiograph, complete metabolic panel, liver function tests, contrast-enhanced CT, and urine cytology performed every 6 to 12 months. If an ileal conduit has been created, vitamin B_{12} levels should also be checked each year. If urethrectomy was not performed at the time of cystectomy, urethral wash cytology should be performed every 6 to 12 months. If patients experience urethral symptoms or are at increased risk for urethral recurrence, urethroscopy may be indicated.

SECTION 10

THERAPEUTICS


H_2O
Systemic circulation
Water drawn into bloodstream from tissues by high osmolality, expanding extracellular volume and causing initial hyponatremia. As free water is excreted, hypernatremia may ensue.
H_2O
H_2O
H_2O
H_2O
Glomerulus
Expansion of extracellular volume leads to increase in renal plasma flow
Proximal convoluted tubule
Na^+ Cl^-
H_2O
Na^+, Cl^-, and water reabsorption decreased throughout nephron
Descending
Loop of Henle
Na^+ Cl^-
H_2O
Ascending
Na^+ Cl^-
Distal convoluted tubule
H_2O
Collecting duct
Water reabsorption from the collecting duct is impaired because the increase in renal plasma flow washes out solute from the medullary interstitium
DIURESIS
Plus nonreabsorbed solute
High Na^+, Cl^-, and K^+
F. Netter M.D.
J. Perkins
MS, MFA

OSMOTIC DIURETICS

ACTIONS AND MECHANISM

In the nephron, water reabsorption is a passive phenomenon that relies on the transcellular osmotic gradients established during the reabsorption of solutes, especially sodium. Osmotic diuretics alter these gradients to produce diuresis. After intravenous administration, such agents undergo filtration at the glomerulus but then cannot be reabsorbed. As sodium and water are reabsorbed, osmotic diuretics become more concentrated in the tubular lumen, eventually generating an osmotic gradient that interferes with further fluid reabsorption. In the proximal tubule, the decreased fluid reabsorption also establishes a transepithelial sodium concentration gradient, normally prevented by the iso-osmotic reabsorption of water, that limits further sodium reabsorption.

In the general circulation, osmotic agents are also restricted to the extracellular space. As a result, fluid shifts from the intracellular to extracellular space, expanding the extracellular volume. An increase in renal blood flow ensues, which is transmitted to the medullary microcirculation and causes solute wash-out from the interstitium. As a result, there is a reduced gradient for water reabsorption from the collecting duct, promoting further water losses.

COMMON AGENTS

The major osmotic diuretic is mannitol, which has a half-life of 0.25 to 1.7 hours and primarily undergoes renal excretion.

INDICATIONS

The most common indications for mannitol include:

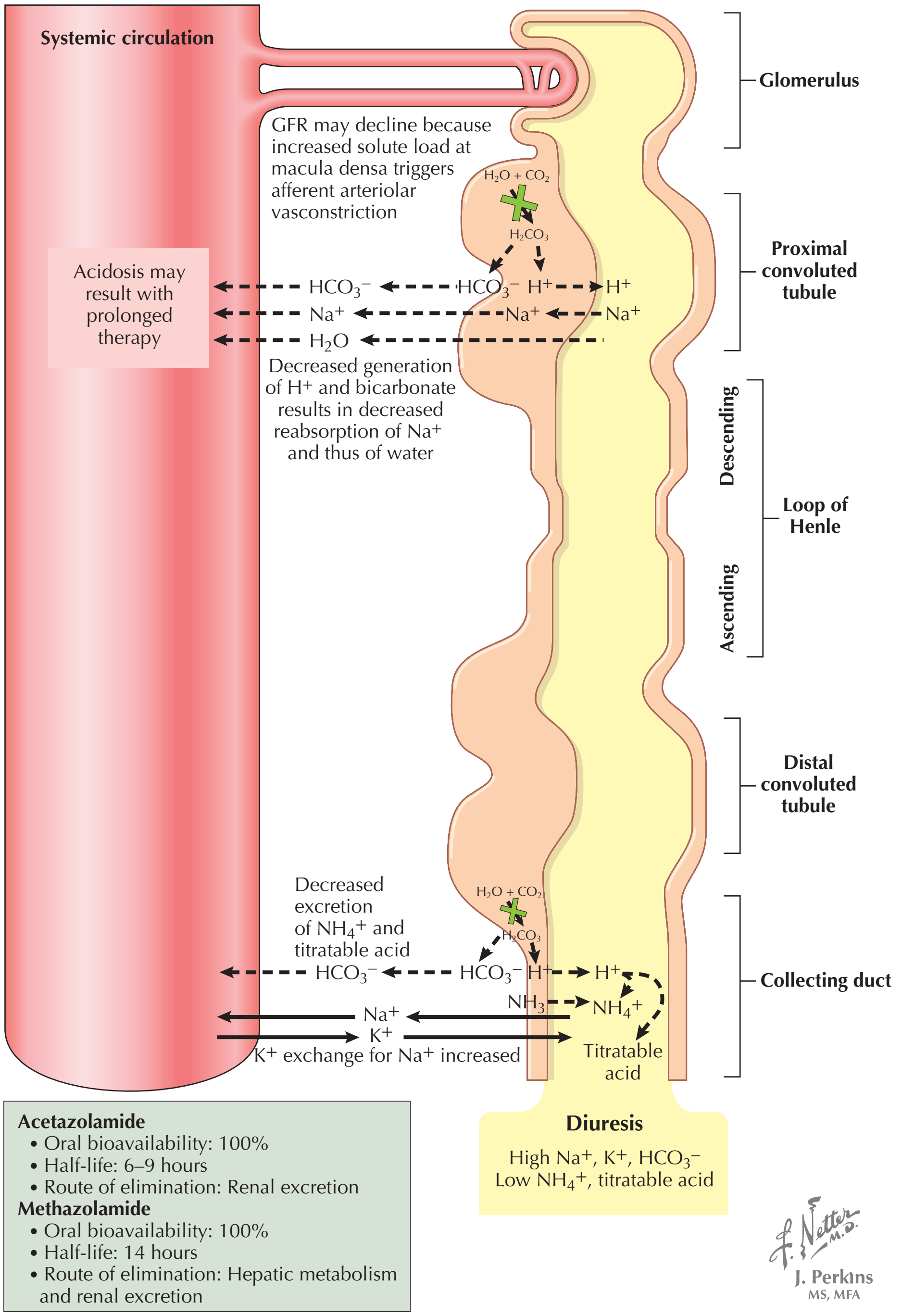
- *Acute kidney injury*, although several randomized controlled studies have found that mannitol offers no benefit in this setting.
- *Cerebral edema*. Mannitol is restricted from the brain by the blood-brain barrier. Therefore, its presence in the general circulation produces an osmotic gradient that promotes a shift of free water from the cerebrospinal fluid to the blood.
- *Acute closed-angle glaucoma*. For the reasons described, mannitol can promote fluid shifts from the eye into the general circulation.

ADVERSE EFFECTS

The major adverse effects of mannitol include:

- *Hyponatremia/hypernatremia*. Osmotic agents are associated with an initial phase of hyponatremia, which results from the systemic efflux of intracellular fluid in response to extracellular hyperosmolality ("pseudohyponatremia"). As free water is excreted with mannitol in the urine, hypernatremia follows, which can cause mental status changes, headache, lethargy, and nausea.
- *Hyperkalemic acidosis*. As water is drawn out of cells, the intracellular concentrations of potassium and protons can rise, prompting their efflux through membrane channels. Hyperkalemic acidosis may persist in patients with poor renal function, who cannot eliminate the excess extracellular potassium or protons.
- *Pulmonary edema* owing to the expansion of extracellular volume

CARBONIC ANHYDRASE INHIBITORS


Systemic circulation
Glomerulus
GFR may decline because increased solute load at macula densa triggers afferent arteriolar vasconstriction
$H_2O + CO_2$
H_2CO_3
Proximal convoluted tubule
Acidosis may result with prolonged therapy
HCO_3^-
HCO_3^- H^+
H^+
Na^+
Na^+
Na^+
H_2O
Decreased generation of H^+ and bicarbonate results in decreased reabsorption of Na^+ and thus of water
Descending
Ascending
Loop of Henle
Distal convoluted tubule
Decreased excretion of NH_4^+ and titratable acid
$H_2O + CO_2$
H_2CO_3
HCO_3^-
HCO_3^- H^+
H^+
NH_3
NH_4^+
Na^+
K^+
K^+ exchange for Na^+ increased
Titratable acid
Collecting duct
Diuresis
High Na^+, K^+, HCO_3^-
Low NH_4^+, titratable acid
F. Netter M.D.
J. Perkins MS, MFA

Acetazolamide
- Oral bioavailability: 100%
- Half-life: 6–9 hours
- Route of elimination: Renal excretion

Methazolamide
- Oral bioavailability: 100%
- Half-life: 14 hours
- Route of elimination: Hepatic metabolism and renal excretion

ACTIONS AND MECHANISM

Carbonic anhydrase (CA) catalyzes the interconversion of carbon dioxide and water to bicarbonate (HCO_3^-) ions and protons. There are multiple CA isoforms, which serve different functions in cells throughout the body. In the renal tubules, the epithelial cells involved in acid-base handling—such as those in the proximal tubule, thick ascending limb, and the cortical collecting duct—possess cytoplasmic CA-II and luminal membrane-bound CA-IV. Several other CA isoforms also appear to be present throughout the nephron, with their locations and functions still under active investigation.

As reviewed in Plates 3-21 and 3-22, CA plays crucial roles in acid-base homeostasis and solute reabsorption. In the proximal tubule, for example, membrane-bound CA-IV catalyzes the conversion of filtered bicarbonate ions and secreted protons into carbon dioxide, which is reabsorbed across the apical surface of proximal tubular cells. Cytoplasmic CA-II, meanwhile, converts the reabsorbed carbon dioxide back into bicarbonate ions, which are reabsorbed, and protons, which are secreted on the NHE-3 Na^+/H^+ exchanger. Meanwhile, in more distal segments, cytoplasmic CA-II converts carbon dioxide to new bicarbonate ions, which are reabsorbed, and protons, which are secreted and bound in the tubular lumen to titratable acids and ammonia.

CA inhibitors (CAIs) are sulfonamide derivatives that block the actions of both cytoplasmic and membrane-bound CA isoforms throughout the nephron. As a result, CAIs cause an increased fraction of the filtered bicarbonate to be excreted, rather than reabsorbed. In addition, these agents impair protonation of titratable acids and ammonia in the distal nephron. Because of these effects, the urine becomes inappropriately alkalotic, and metabolic acidosis ensues.

In addition to their effects on acid-base equilibrium, CAIs also impair proximal Na^+ reabsorption, since operation of the NHE-3 exchanger depends on the presence of protons in the cytoplasm of tubular epithelial cells. The natriuretic effect of this action, however, is largely offset by upregulation of distal Na^+ reabsorption sites, such as the thick ascending limb, that possess proton-independent Na^+ transport mechanisms. Moreover, the increased solute load delivered to the macula densa stimulates afferent arteriolar vasoconstriction, reducing the glomerular filtration rate.

Because CA is widely distributed through the body, CAIs have multiple extrarenal effects that render them useful in other clinical settings. In the ciliary processes of the eye, for example, CAIs reduce the production of aqueous humor, making them effective agents in the treatment of glaucoma.

COMMON AGENTS

The major CAIs are listed in the plate.

INDICATIONS

The most common indications for CAIs include:

- *Edema*, but they are rarely given for this indication because other diuretic classes are safer and more effective.
- *Acute mountain sickness*. At high altitudes, the low partial pressure of oxygen induces hyperventilation. This response improves tissue oxygenation but is limited by the ensuing respiratory alkalosis. Acetazolamide can be used to induce metabolic acidosis and further increase ventilation.
- *Open- or closed-angle glaucoma*. As described above, CAIs reduce production of aqueous humor in the anterior chamber of the eye. Methazolamide is preferred for this indication because of its long half-life. In closed-angle glaucoma, CAIs can be used as a temporizing measure until definitive treatment is available.

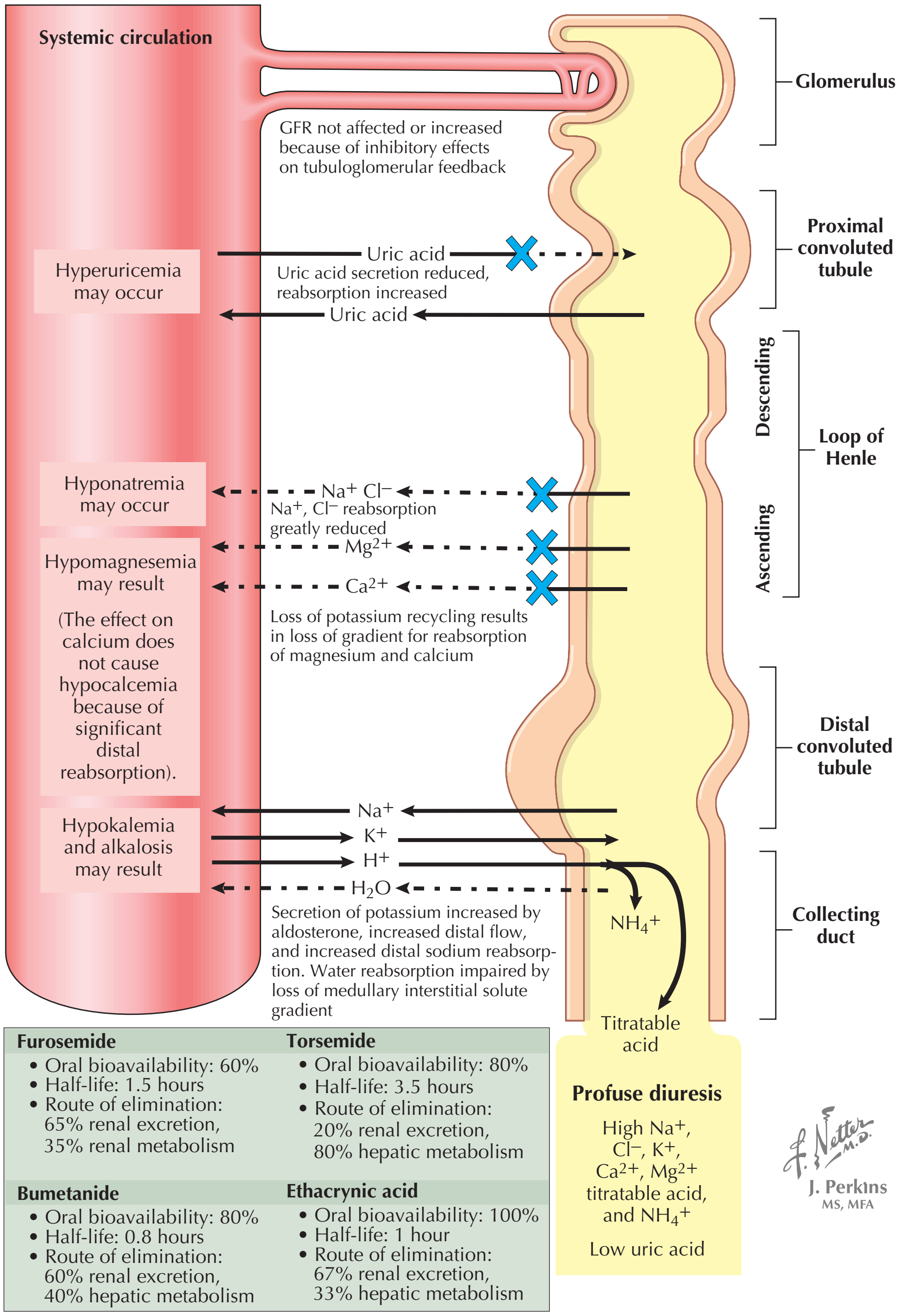
ADVERSE EFFECTS

The major adverse effects of CAIs include:

- *Metabolic acidosis*
- *Nephrolithiasis*, owing to urine alkalinization
- *Increased serum ammonia concentration*, secondary to impaired renal excretion, which may cause encephalopathy in patients with cirrhosis
- *Bone marrow suppression*
- *Skin toxicity*
- *Confusion, drowsiness, and paresthesia*, secondary to central nervous system effects

CAIs increase K^+ excretion in several ways. First, the increased Na^+ load that reaches the distal nephron creates a negative intraluminal charge as it is reabsorbed, which promotes K^+ secretion through apical renal outer medullary potassium (ROM-K) channels. Second, the increased HCO_3^- load that reaches the distal nephron also generates a negative intraluminal charge, which promotes K^+ secretion for the same reasons. Finally, the increased urine flow through the distal nephron promotes K^+ secretion through flow-sensitive maxi-K channels. Such kaliuresis, however, rarely leads to hypokalemia because metabolic acidosis stimulates K^+ efflux from cells in exchange for H^+ influx.

LOOP DIURETICS


Systemic circulation
Glomerulus
GFR not affected or increased because of inhibitory effects on tubuloglomerular feedback
Proximal convoluted tubule
Hyperuricemia may occur
Uric acid
Uric acid secretion reduced, reabsorption increased
Uric acid
Descending
Ascending
Loop of Henle
Hyponatremia may occur
Na+ Cl−
Na+, Cl− reabsorption greatly reduced
Hypomagnesemia may result
Mg2+
Ca2+
(The effect on calcium does not cause hypocalcemia because of significant distal reabsorption).
Loss of potassium recycling results in loss of gradient for reabsorption of magnesium and calcium
Distal convoluted tubule
Hypokalemia and alkalosis may result
Na+
K+
H+
H2O
NH4+
Secretion of potassium increased by aldosterone, increased distal flow, and increased distal sodium reabsorption. Water reabsorption impaired by loss of medullary interstitial solute gradient
Collecting duct
Titratable acid
Profuse diuresis
High Na+, Cl−, K+, Ca2+, Mg2+ titratable acid, and NH4+
Low uric acid
F. Netter M.D.
J. Perkins MS, MFA

Furosemide
- Oral bioavailability: 60%
- Half-life: 1.5 hours
- Route of elimination: 65% renal excretion, 35% renal metabolism

Torsemide
- Oral bioavailability: 80%
- Half-life: 3.5 hours
- Route of elimination: 20% renal excretion, 80% hepatic metabolism

Bumetanide
- Oral bioavailability: 80%
- Half-life: 0.8 hours
- Route of elimination: 60% renal excretion, 40% hepatic metabolism

Ethacrynic acid
- Oral bioavailability: 100%
- Half-life: 1 hour
- Route of elimination: 67% renal excretion, 33% hepatic metabolism

ACTIONS AND MECHANISM

In the thick ascending limb (TAL), Na^+, K^+, and Cl^- are reabsorbed across the apical surface of the tubular epithelium on NKCC2 transporters. Such reabsorption is essential for the maintenance of a high medullary interstitial solute gradient, which permits urine concentration in the collecting duct (see Plate 3-15). In addition, recycling of the reabsorbed potassium back into the lumen through apical ROMK channels establishes the positive intraluminal charge required for reabsorption of Ca^{2+} and Mg^{2+} (see Plate 3-11).

Loop diuretics enter the nephron through the organic anion secretion pathway in the proximal tubule, then they bind to the apical surface of NKCC2 transporters and inhibit their function.

Because the distal nephron is unable to reabsorb the large sodium load rejected from the thick ascending limb, the diuresis associated with these drugs is profound. In addition, loop diuretics also have weak diuretic effects elsewhere in the nephron. In the proximal tubule, for example, some loop diuretics weakly inhibit carbonic anhydrase. Meanwhile, in the distal nephron, some loop diuretics weakly inhibit the thiazide-sensitive NCC Na^+/Cl^- symporter.

Loop diuretics also influence the excretion of several other ions. The reabsorption of both Ca^{2+} and Mg^{2+} is decreased because of the reduction in K^+ recycling in the TAL. In addition, loop diuretics both increase uric acid reabsorption (by promoting fluid losses, which enhances proximal uric acid reabsorption) and decrease uric acid secretion (by competing with it at the organic anion secretion pathway). Finally, loop diuretics promote K^+ secretion through various mechanisms. First, the increased Na^+ load that reaches the cortical collecting duct creates a negative intraluminal charge as it is reabsorbed, promoting K^+ secretion through apical ROM-K channels. Second, the increased urine flow through the cortical collecting duct upregulates flow-sensitive maxi-K channels.

Because NKCC2 transporters have an essential role in tubuloglomerular feedback and the regulation of renin secretion, loop diuretics also affect both of these processes. As shown in Plate 3-18, a reduction in NKCC2 transport is normally associated with a reduction in the glomerular filtration rate (GFR) because a slower urine flow rate allows the proximal tubule to capture a greater fraction of the filtered ions. The normal response to a reduction in NKCC2 transport is dilation of the afferent arteriole, which normalizes the glomerular filtration rate, and release of renin, which activates the renin-angiotensin-aldosterone system.

In the presence of a loop diuretic, NKCC2 transport is blocked. As a result, there is chronic dilation of the afferent arteriole despite high flow rates through the nephron, which enhances fluid losses. In addition, there is chronic secretion of renin, which leads to increased synthesis of angiotensin and aldosterone. The result is a further increase in K^+ secretion, which contributes to the development of hypokalemia, and an increase in H^+ secretion, which can result in metabolic alkalosis.

The efficacy of loop diuretics can become limited over repeated doses for several reasons. In part, this effect occurs because the distal nephron increases its reabsorptive capacity, blunting the efficacy of loop diuretics and markedly increasing salt retention between doses. Therefore, to maximize the response to a loop diuretic, patients should be maintained on a low-salt diet, dosed frequently enough to limit the time available for postdiuretic salt retention, and offered simultaneous treatment with drugs that target the distal nephron, such as thiazides.

COMMON AGENTS

The major loop diuretics are listed in the plate.

INDICATIONS

The major indications for loop diuretics include:
- *Peripheral or pulmonary edema*
- *Hypertension*

ADVERSE EFFECTS

The major adverse effects of thiazide diuretics include:
- *Ototoxicity*, manifest as tinnitus, vertigo, or hearing loss
- *Hypokalemia*
- *Hypomagnesemia*
- *Hyponatremia*. By inhibiting solute reabsorption in the TAL, loop diuretics prevent maximal urine dilution. In addition, significant fluid losses can trigger release of antidiuretic hormone (see Plate 3-17)
- *Hyperuricemia*, which may precipitate gout attacks
- *Hypotension*, if excessive extracellular fluid is lost
- *Metabolic alkalosis*, resulting from aldosterone release secondary to volume losses and, if hypokalemia is present, an increase in proximal tubular ammoniagenesis
- *Impaired glucose tolerance or diabetes mellitus* secondary to multiple mechanisms, including catecholamine release (secondary to activation of the sympathetic nervous system resulting from volume depletion), as well as reduced insulin secretion (secondary to hypokalemia)
- *Hyperlipidemia*, through mostly unknown mechanisms
- *Photosensitivity*
- *Paresthesia*

THIAZIDE DIURETICS

ACTIONS AND MECHANISM

In the distal convoluted tubule, Na$^+$ and Cl$^-$ are reabsorbed across the apical surface of the tubular epithelium on NCC symporters. The thiazide diuretics enter the nephron through the organic anion pathway in the proximal tubule, then they bind to the apical surface of NCC symporters and inhibit them.

Because the vast majority of Na$^+$ reabsorption occurs in earlier nephron segments, particularly the proximal tubule and thick ascending limb, thiazides induce only a modest degree of natriuresis. Some agents, however, are also weak carbonic anhydrase inhibitors (see Plate 10-2) and thus partially inhibit Na$^+$ reabsorption in the proximal tubule.

Thiazides also affect the handling of several other ions. For example, they promote kaliuresis through numerous mechanisms. First, the increased Na$^+$ load that reaches the cortical collecting duct leaves a negative charge in the lumen as it is reabsorbed, which promotes K$^+$ secretion through apical ROM-K channels. Second, the increased urine flow through the cortical collecting duct up-regulates apical maxi-K channels. Finally, volume losses lead to aldosterone release, which further increases distal K$^+$ (and H$^+$) secretion.

Thiazides also enhance calcium reabsorption through several mechanisms. First, blockade of NCC transport decreases intracellular Na$^+$ concentrations, increasing the gradient for basolateral Na$^+$/Ca^{2+} exchange. Second, volume losses stimulate reabsorption of Na$^+$ and Cl$^-$ in the proximal tubule, enhancing the gradient for paracellular calcium reabsorption. (For a detailed discussion of calcium handling in the nephron, see Plate 3-11.) Thiazides also inhibit magnesium reabsorption, likely by interfering with TRPM6-mediated reabsorption in the distal nephron, although the exact mechanism remains unknown.

Finally, thiazides decrease excretion of uric acid. Like the loop diuretics, thiazides likely exert this effect by increasing proximal tubular reabsorption (secondary to fluid depletion) and decreasing proximal tubular secretion (by competing with uric acid on the organic cation secretion pathway).

COMMON AGENTS

The major thiazide and thiazide-like diuretics are listed in the plate.

INDICATIONS

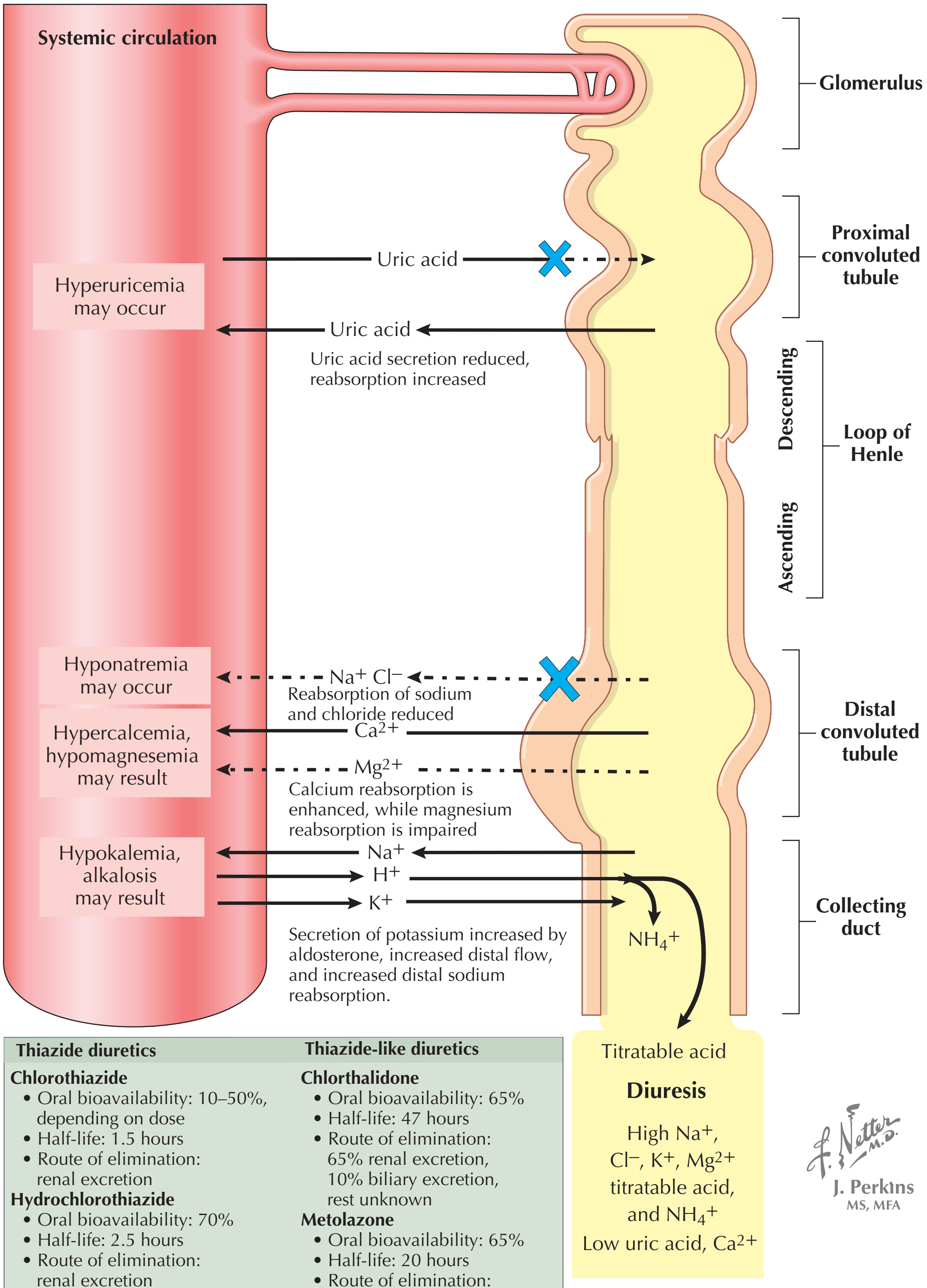
The major indications for thiazide diuretics include:

- *Edema*
- *Hypertension*
- *Hypocalcemia*
- *Hypercalciuria* with recurrent formation of calcium stones (see Plate 6-3)
- *Diabetes insipidus* (see Plate 3-27)

ADVERSE EFFECTS

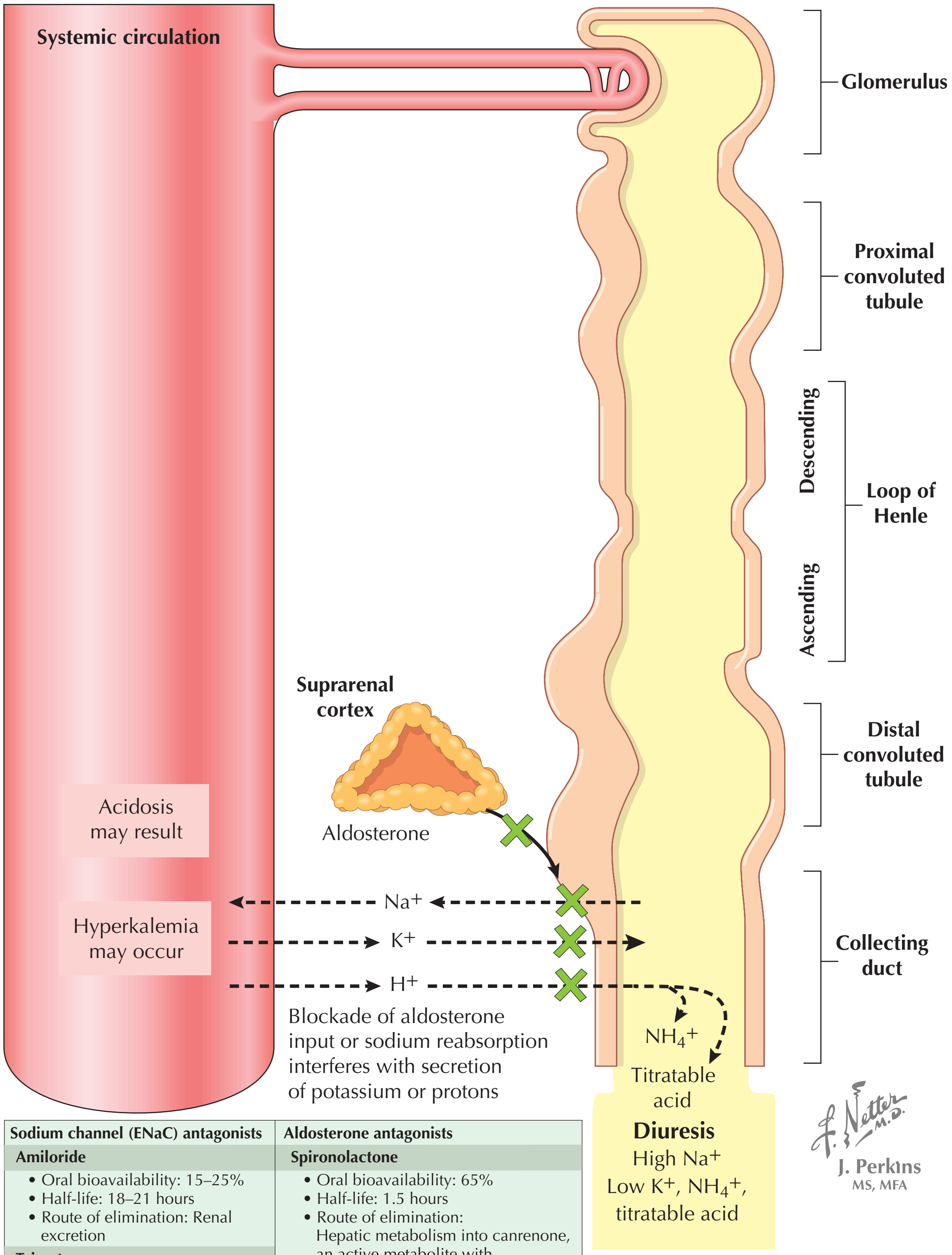
The major adverse effects of thiazide diuretics include:

- *Hypokalemia*
- *Hyponatremia*. By inhibiting solute reabsorption in the distal nephron, thiazides prevent maximal urine dilution. In addition, significant fluid losses can trigger release of antidiuretic hormone (see Plate 3-17).
- *Hypercalcemia*
- *Hypomagnesemia* (with long-term use)
- *Hyperuricemia*, which may precipitate gout attacks
- *Metabolic alkalosis*, resulting from aldosterone release secondary to volume losses and, if hypokalemia is present, an increase in proximal tubular ammoniagenesis
- *Impaired glucose tolerance or diabetes mellitus* secondary to multiple mechanisms, including catecholamine release (secondary to activation of the sympathetic nervous system resulting from volume depletion), as well as reduced insulin secretion (secondary to hypokalemia)
- *Hyperlipidemia*, through mostly unknown mechanisms
- *Nausea and vomiting*
- *Photosensitivity*
- *Erectile dysfunction*


Systemic circulation
Glomerulus
Proximal convoluted tubule
Hyperuricemia may occur
Uric acid
Uric acid
Uric acid secretion reduced, reabsorption increased
Descending
Ascending
Loop of Henle
Hyponatremia may occur
Na+ Cl–
Reabsorption of sodium and chloride reduced
Hypercalcemia, hypomagnesemia may result
Ca2+
Mg2+
Calcium reabsorption is enhanced, while magnesium reabsorption is impaired
Distal convoluted tubule
Hypokalemia, alkalosis may result
Na+
H+
K+
NH4+
Secretion of potassium increased by aldosterone, increased distal flow, and increased distal sodium reabsorption.
Collecting duct
Titratable acid
Diuresis
High Na+, Cl–, K+, Mg2+ titratable acid, and NH4+
Low uric acid, Ca2+
J. Perkins MS, MFA

Thiazide diuretics	**Thiazide-like diuretics**
Chlorothiazide • Oral bioavailability: 10–50%, depending on dose • Half-life: 1.5 hours • Route of elimination: renal excretion	**Chlorthalidone** • Oral bioavailability: 65% • Half-life: 47 hours • Route of elimination: 65% renal excretion, 10% biliary excretion, rest unknown
Hydrochlorothiazide • Oral bioavailability: 70% • Half-life: 2.5 hours • Route of elimination: renal excretion	**Metolazone** • Oral bioavailability: 65% • Half-life: 20 hours • Route of elimination: 80% renal excretion, 10% biliary excretion, 10% hepatic metabolism

POTASSIUM-SPARING DIURETICS



Sodium channel (ENaC) antagonists	Aldosterone antagonists
Amiloride	**Spironolactone**
• Oral bioavailability: 15–25% • Half-life: 18–21 hours • Route of elimination: Renal excretion	• Oral bioavailability: 65% • Half-life: 1.5 hours • Route of elimination: Hepatic metabolism into canrenone, an active metabolite with a half-life of ~16 hours
Triamterene	**Eplerenone**
• Oral bioavailability: 50% • Half-life: 3–5 hours • Route of elimination: Hepatic metabolism to an active metabolite, which is excreted in urine	• Oral bioavailability: Unknown • Half-life: 3–5 hours • Route of elimination: Hepatic metabolism

ACTIONS AND MECHANISM

In the connecting tubule and cortical collecting duct, principal cells are responsible for K^+ secretion through two major mechanisms. First, the reabsorption of Na^+ through apical ENaC channels leaves a negative charge in the tubular lumen, which promotes the secretion of potassium through apical ROM-K channels. Second, increased flow rates through the distal nephron stimulate K^+ secretion through apical maxi-K channels.

Most diuretics—including carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics—up-regulate distal K^+ secretion through several mechanisms. First, these agents interfere with Na^+ reabsorption in more proximal portions of the nephron, which increases the load that reaches the distal nephron. The increased Na^+ gradient across the apical surface of principal cells increases reabsorption through ENaC channels, which then leads to increased K^+ secretion through ROMK channels. Second, these agents cause volume loss, which activates the renin-angiotensin-aldosterone system. One of aldosterone's effects is to up-regulate ENaC channels, which increases Na^+ reabsorption and, by necessity, also increases K^+ excretion. Finally, diuretics increase urine flow rates through the distal nephron, which stimulates K^+ secretion through apical maxi-K channels.

The "potassium-sparing" diuretics interfere with sodium reabsorption across ENaC channels, which produces a small diuretic effect and, more importantly, eliminates one of the major causes of K^+ secretion. This category of diuretics encompasses two different classes of agents: those that directly block the ENaC channel (amiloride and triamterene) and those that block aldosterone signaling (spironolactone and eplerenone).

ENaC channel blockers enter the nephron through the organic cation pathway in the proximal tubule. Upon reaching principal cells, these agents bind to the ENaC channel from its luminal side, competing with Na^+ ions for negatively charged sites in the pore. Meanwhile, aldosterone receptor blockers remain in the plasma to act at the basolateral surface of principal cells.

Potassium-sparing diuretics usually have only a small diuretic effect. Nonetheless, they can be useful in combination with other classes of diuretics because of their effects on potassium homeostasis. They can also help offset the increase in distal sodium reabsorption that occurs with the use of other diuretics.

COMMON AGENTS

The major potassium-sparing diuretics are listed in the plate.

INDICATIONS

The major indications for potassium-sparing diuretics include:

- *Hypokalemia*, especially if associated with the use of another diuretic
- *Liddle syndrome* (ENaC blockers)
- *Primary hyperaldosteronism* (aldosterone antagonists)
- *Congestive heart failure* (aldosterone antagonists)
- *Ascites* (aldosterone antagonists)

ADVERSE EFFECTS

The major adverse effects of potassium-sparing diuretics include:

- *Hyperkalemia*
- *Metabolic acidosis*. Through the same mechanisms used to reduce K^+ secretion, these agents also reduce H^+ secretion into the distal nephron.
- *Acute kidney injury* (triamterene, owing to crystalluria and tubular obstruction)
- *Nausea, vomiting, and diarrhea*
- *Peptic ulcers* (spironolactone)
- *Headache and lethargy*
- *Rash*
- *Antiandrogenic effects*: gynecomastia and/or breast pain, impotence, hirsutism, and irregular menses (aldosterone antagonists, spironolactone more than eplerenone)

INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

As shown on Plate 3-19, the renin-angiotensin system plays an essential role in the regulation of systemic blood pressure. In brief, renin is released from juxtaglomerular cells in response to decreased renal tubular flow, sympathetic input, or decreased stretch of afferent arterioles. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is rapidly converted by angiotensin-converting enzyme (ACE) into angiotensin II (AII). AII increases blood pressure through direct vasoconstrictor effects on systemic vessels and through various other mechanisms, including increased sodium reabsorption from the renal tubules, potentiation of sympathetic tone, and stimulation of aldosterone and antidiuretic hormone release.

Several agents can inhibit this system, including ACE inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors. These agents are powerful antihypertensive medications, but they are also capable of slowing the progression of renal disease. The mechanism by which these agents protect the kidneys is not fully known, but it likely relates in part to their effects on glomerular hemodynamics. Whenever renal disease causes nephron loss, there is compensatory hyperfiltration of the remaining nephrons that is mediated, at least in part, by AII-dependent constriction of efferent arterioles. Although this response allows the kidneys to temporarily maintain high levels of filtration function, it is ultimately maladaptive because the high intraglomerular pressure causes capillary wall damage, leading to worsening proteinuria and glomerulosclerosis. By relieving constriction of the efferent arterioles, these drugs lower intraglomerular pressure, reducing proteinuria and protecting the glomerular capillary walls. Although this effect is renoprotective in the long term, it is associated with a reversible and expected 20% to 30% decline in glomerular filtration rate (GFR) at the onset of drug therapy, especially if other diuretics are also used. In most patients, however, this effect should not be a reason to stop treatment.

INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

ACE inhibitors

Captopril
- Structure: Sulfhydryl-containing
- Oral bioavailability: 75%
- Half-life: 2 hours
- Route of elimination: Renal excretion

Benazepril
- Structure: Carboxyl-containing prodrug that is converted into benazeprilat, an active metabolite
- Oral bioavailability: 37%
- Half-life (of benazeprilat): 22 hours
- Route of elimination: Renal and biliary excretion

Enalapril
- Structure: Carboxyl-containing prodrug that is converted into enalaprilat, an active metabolite
- Oral bioavailability: 60–70%
- Half-life (of enalaprilat): 11 hours
- Route of elimination: Renal excretion

Lisinopril
- Structure: Carboxyl-containing
- Oral bioavailability: 30%
- Half-life: 12 hours
- Route of elimination: Renal excretion

Quinipril
- Structure: Carboxyl-containing prodrug that is converted into quinaprilat, an active metabolite
- Oral bioavailability: 50%
- Half-life (of quiniprilat): 25 hours
- Route of elimination: Renal and biliary excretion

Ramipril
- Structure: Carboxyl-containing prodrug that is converted into ramiprilat, an active metabolite
- Oral bioavailability: 60%
- Half-life (of ramiprilat): 10–17 hours
- Route of elimination: Renal and biliary excretion

Fosinopril
- Structure: Phosphinyl-containing prodrug that is converted into fosinoprilat, an active metabolite
- Oral bioavailability: 36%
- Half-life (of fosinoprilat): 11.5 hours
- Route of elimination: Renal and biliary excretion

Angiotensin receptor (AT1) blockers

Losartan
- Mode of action: competitive inhibitor
- Oral bioavailability: 25%
- Half-life: 4–9 hours
- Route of elimination: Renal and biliary excretion

Candesartan cilexitil (converted into candesartan during intestinal absorption)
- Mode of action: non-competitive inhibitor
- Oral bioavailability: 15%
- Half-life: 9 hours
- Route of elimination: Renal and biliary excretion

Irbesartan
- Mode of action: non-competitive inhibitor
- Oral bioavailability: 60–80%
- Half-life: 10–15 hours
- Route of elimination: Renal and biliary excretion

Olmesartan medoxomil (converted into olmesartan during intestinal absorption)
- Mode of action: competitive inhibitor
- Oral bioavailability: 25%
- Half-life: 12–18 hours
- Route of elimination: Renal and biliary excretion

Eprosartan
- Mode of action: non-competitive inhibitor
- Oral bioavailability: 13%
- Half-life: 6–9 hours
- Route of elimination: Renal and biliary excretion

Telmisartan
- Mode of action: non-competitive inhibitor
- Oral bioavailability: 42%
- Half-life: 24 hours
- Route of elimination: Biliary excretion

Valsartan
- Mode of action: non-competitive inhibitor
- Oral bioavailability: 25%
- Half-life: 9 hours
- Route of elimination: Renal and biliary excretion

Direct renin inhibitors

Aliskiren
- Oral bioavailability: 2.6%
- Half-life: 27 hours
- Route of elimination: Biliary excretion

ACE INHIBITORS

ACE inhibitors prevent the ACE-mediated conversion of angiotensin I to angiotensin II, thereby interfering with the latter's prohypertensive effects. These agents also inhibit other ACE-mediated pathways, which may contribute to their clinical effect. For example, they also inhibit the metabolism of bradykinins, which promote vasodilation and upregulate prostaglandin synthesis.

ACE inhibitors can be broadly classified as sulfhydryl-containing, carboxyl-containing, or phosphinyl-containing. In addition, some of these agents directly block ACE, whereas others must first undergo transformation into active metabolites.

The major indications for ACE inhibitors are:
- *Hypertension*, especially in patients with congestive heart failure, diabetes mellitus, and, or renal insufficiency
- *Systolic left ventricular dysfunction*, since these agents reduce afterload and inhibit ventricular remodeling
- *Chronic kidney disease*

The major adverse effects of ACE inhibitors include:
- *Cough*, owing to increased levels of bradykinin and prostaglandins
- *Angioedema*, also thought to be bradykinin-mediated
- *Hypotension*, generally at the onset of drug treatment
- *Hyperkalemia*, owing to reduced aldosterone levels, especially when used in combination with a potassium-sparing diuretic
- *Acute kidney injury*. Although some decline in GFR is expected, patients with renal artery stenosis (see Plate 4-36) may experience renal failure because they require efferent arteriolar constriction to maintain adequate hydrostatic pressure in the glomerular capillaries
- *Dysgeusia*, especially with captopril
- *Maculopapular, sometimes pruritic rash*
- *Neutropenia*, especially in those with renal insufficiency or autoimmune disease

ANGIOTENSIN II RECEPTOR BLOCKERS

The ARBs are a class of competitive and noncompetitive antagonists of the AT1 angiotensin receptor. These agents are very similar to ACE inhibitors, but they do differ in several important respects. First, because they do not interfere with bradykinin metabolism, these agents are associated with a much smaller risk of cough and angioedema. Second, ARBs are theoretically more potent than ACE inhibitors because they can inhibit the small amount of AII produced through ACE-independent mechanisms. Third, ARBs block AT1 receptors but not AT2 receptors, although the significance of this difference is unclear.

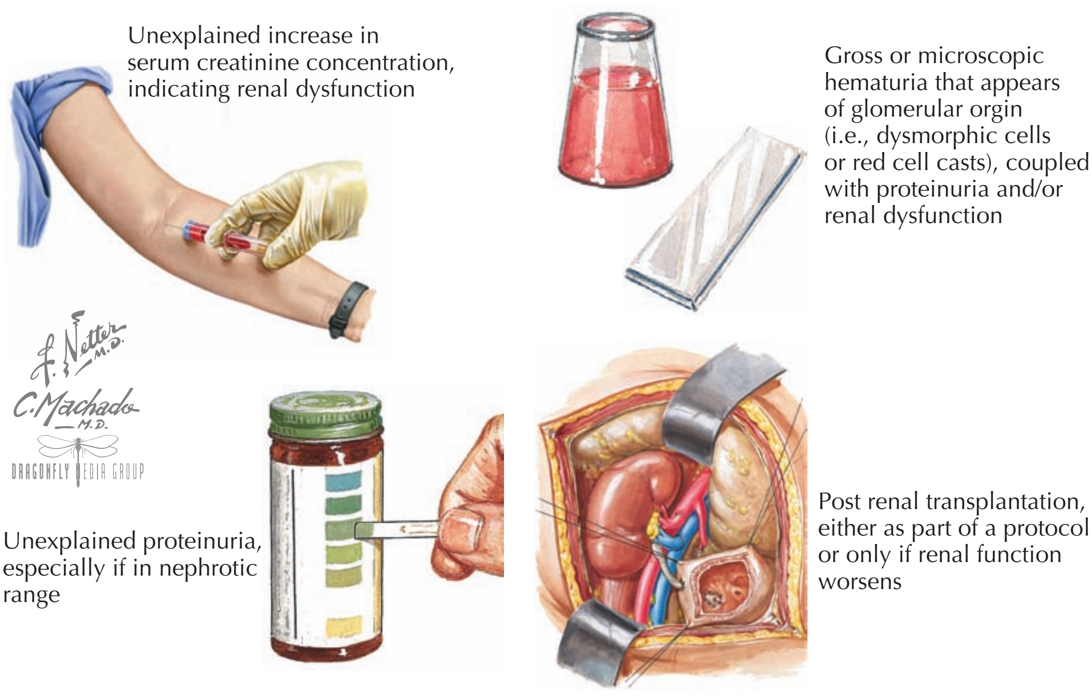
The indications for ARBs are essentially the same as those for ACE inhibitors. In many instances, patients are started on ARBs if they are unable to tolerate the coughing associated with ACE inhibitors. The major adverse effects of ARBs include angioedema (although to a lesser extent than with ACE inhibitors), hyperkalemia, and acute kidney injury, all of which occur through the same mechanisms as with ACE inhibitors.

DIRECT RENIN INHIBITORS

The direct renin inhibitors (DRIs) block the conversion of angiotensinogen, renin's only known substrate, to angiotensin I. Thus, unlike ACE inhibitors, these agents can effectively block the non-ACE conversion of angiotensin I to angiotensin II, and they do not interfere with bradykinin metabolism. Unlike ARBs, they also prevent AT2 receptor-mediated signaling. These drugs have been associated with a reduction of proteinuria in combination with ACE inhibitors and ARBs. Their adverse effect profile appears to be similar to that of ARBs.

RENAL BIOPSY: INDICATIONS AND STRUCTURE OF TYPICAL SPRING-LOADED NEEDLE

Common indications



Unexplained increase in serum creatinine concentration, indicating renal dysfunction

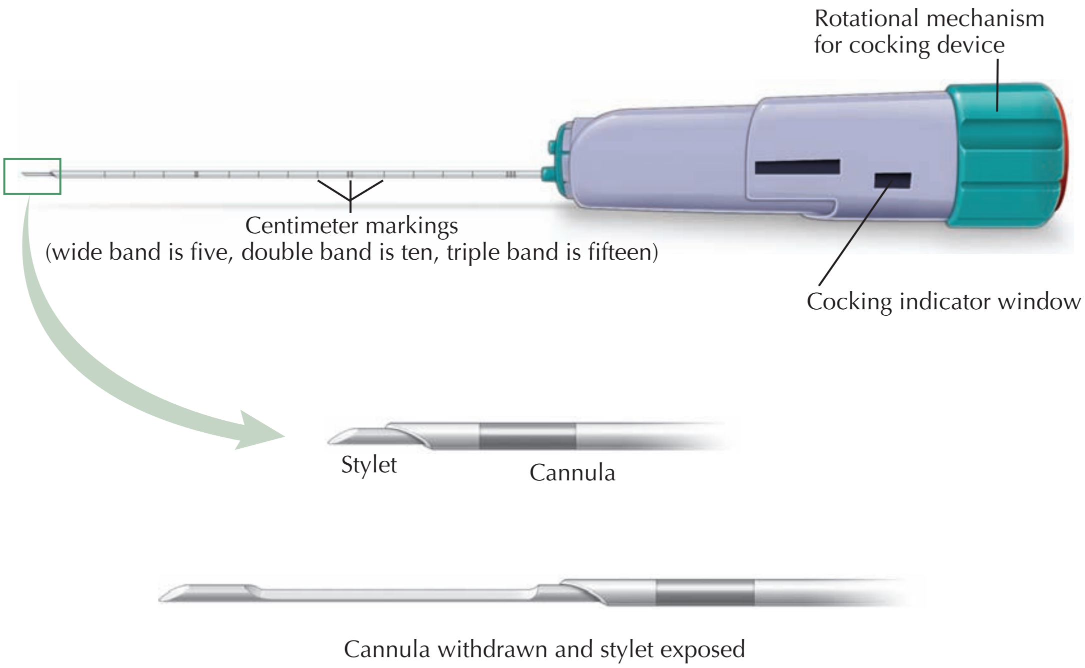
Gross or microscopic hematuria that appears of glomerular orgin (i.e., dysmorphic cells or red cell casts), coupled with proteinuria and/or renal dysfunction

Unexplained proteinuria, especially if in nephrotic range

Post renal transplantation, either as part of a protocol or only if renal function worsens

Structure of typical spring-loaded biopsy needle

Various biopsy devices are available with different needle widths and lengths.


Rotational mechanism for cocking device
Centimeter markings
(wide band is five, double band is ten, triple band is fifteen)
Cocking indicator window
Stylet
Cannula
Cannula withdrawn and stylet exposed

RENAL BIOPSY

A renal biopsy yields a small piece of renal parenchyma for histopathologic examination. Because many renal diseases have essentially indistinguishable clinical findings, renal biopsy is often crucial for establishing the correct diagnosis and devising an effective treatment plan. The procedure is generally uncomplicated and, in most cases, can safely be performed by a nephrologist at the bedside.

INDICATIONS

The major indications for renal biopsy include renal failure of unknown cause, proteinuria, hematuria, and renal transplantation.

Proteinuria. In patients with mild proteinuria (1 to 2 g/day) that has no obvious cause, such as diabetes mellitus, a renal biopsy may be performed to establish a definitive diagnosis. The exact threshold for biopsy differs across practitioners and depends on individual clinical judgment. Possible causes of this degree of proteinuria include glomerulonephritis and mild forms of the diseases that typically cause nephrotic syndrome, such as focal segmental glomerulosclerosis (FSGS) or membranous nephropathy (MN). Although tubulointerstitial disease commonly causes mild proteinuria, a biopsy is generally not required to establish the diagnosis.

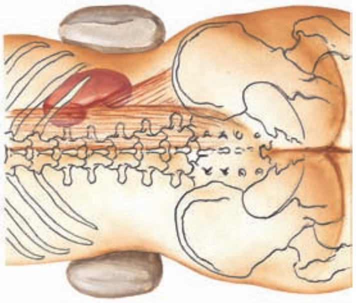
In patients with nephrotic-range proteinuria (i.e., >3 g/day), a renal biopsy is indicated to identify the disease process, guide treatment, and determine prognosis. Possible causes of nephrotic-range proteinuria include primary or secondary FSGS, MN, minimal change disease (MCD), and (rarely) fibrillary or immunotactoid glomerulonephritis. If, however, the patient has a diagnosed systemic illness that is known to cause nephrotic syndrome, a renal biopsy is typically not required. Examples include patients with long-standing diabetes mellitus and concurrent diabetic retinopathy, or patients with amyloidosis seen on a biopsy of another affected organ system. In addition, young children with nephrotic syndrome are generally presumed to have MCD, with a renal biopsy only performed if empiric treatment for this condition fails.

Hematuria. In patients with gross or microscopic hematuria, the initial workup should focus on urologic abnormalities, such as nephrolithiasis, neoplasm, or infection. The presence of dysmorphic red cells, proteinuria, and renal insufficiency, however, strongly points toward glomerular disease. Many renal diseases are associated with microscopic hematuria, including essential hematuria, acute interstitial nephritis, IgA nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, cryoglobulinemia, fibrillary/immunotactoid glomerulonephritis, ANCA-associated vasculitis, malignant hypertension, atheroembolic renal disease, renal infarction, thrombotic microangiopathy, Henoch-Schönlein purpura, thin basement membrane nephropathy, hereditary nephritis, and anti-GBM disease. A kidney biopsy is essential for establishing the correct diagnosis and determining an optimal treatment plan.

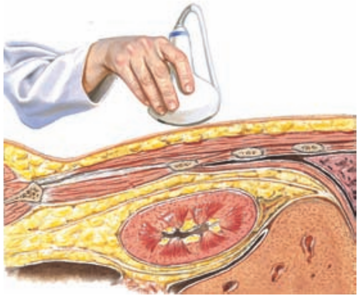
Occasionally, patients may have isolated hematuria (i.e., without proteinuria or renal insufficiency). The differential diagnosis for such patients includes thin basement membrane disease, mild IgA nephropathy, and hereditary nephritis. A kidney biopsy is typically not performed, however, because treatment is not instituted unless there is significant proteinuria or renal insufficiency.

Renal transplant. Patients who have undergone renal transplant and subsequently develop renal failure should have a biopsy if their renal function does not improve after provision of intravenous fluids. In such circumstances, a biopsy is helpful for differentiating between various entities, such as acute or chronic

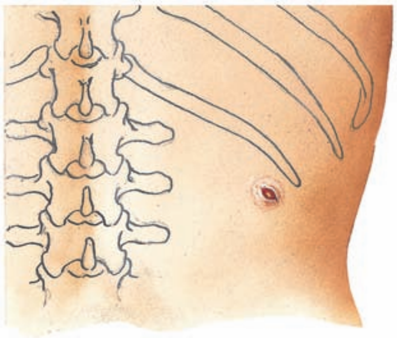
RENAL BIOPSY: PROCEDURE



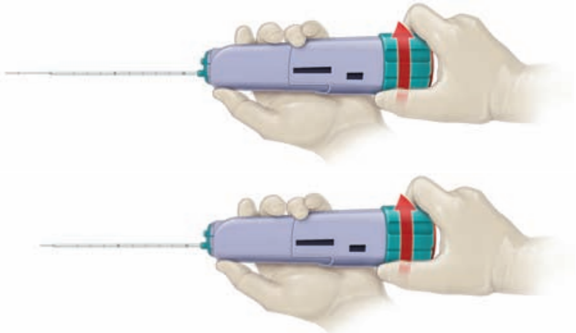
1. Patient positioned prone in bed, with folded pillow under abdomen. **2.** Approximate location of kidney is determined by palpation of bone structures.



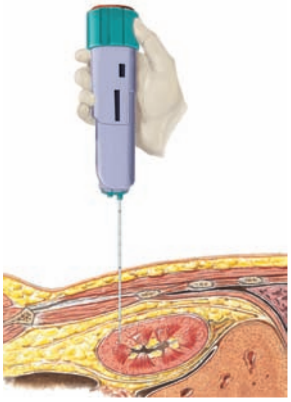
3. Ultrasound is used to locate kidney and determine optimal site and angle of needle insertion. The needle tip should aim toward the pole so only cortical tissue is biopsied.



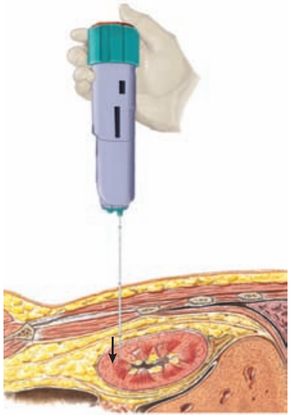
4. The site is sterilized and anesthetized. For larger gauge needles, a scalpel may be used to make a small incision at the site of planned needle entry.



5. The biopsy needle is cocked. The first twist retracts the cannula. The second twist retracts the stylet.



6. The biopsy needle is inserted. When the tip is in the renal parenchyma, the needle will be deflected by the movement of the kidney during respiration. Proper positioning may also be confirmed using ultrasound guidance.



7. Once proper positioning is confirmed, the actuator is depressed, causing the stylet and cannula to rapidly advance into the parenchyma. The needle is then withdrawn.

RENAL BIOPSY *(Continued)*

rejection, drug toxicity (especially from calcineurin inhibitors), and BK virus infection. Some centers also routinely take biopsies from transplanted kidneys at predetermined time points, even in the absence of overt dysfunction because some renal disease may initially be clinically silent.

PROCEDURE

Before a patient undergoes a renal biopsy, anticoagulation medications should be stopped, and bleeding risk should be evaluated by obtaining a prothrombin time, partial thromboplastin time, and platelet count. Any bleeding diathesis should be corrected, if possible, before the procedure.

Most patients can undergo a percutaneous biopsy, which is performed at the bedside; however, select patients may require alternate approaches, including open, laparoscopic, and transjugular biopsies. The major indications for these techniques include an uncorrectable bleeding diathesis, morbid obesity, solitary kidney, infection of the skin over the kidneys, and failed percutaneous attempts.

For a percutaneous biopsy, most patients should be placed prone, with a folded pillow under the abdomen. An ultrasound is performed to visualize the kidney and determine the location and angle of needle insertion. The upper or lower pole should be targeted so that only cortical tissue is acquired. Hydronephrosis, multiple cysts, or small hyperechoic kidneys may be seen, which increase the bleeding risk and should be considered relative contraindications.

Once the initial ultrasound is complete, the site is dressed and draped in normal sterile fashion. The site is injected with a local anesthetic, and a scalpel may be used to nick the skin at the area of planned needle insertion. The biopsy needle, which consists of a spring-loaded outer cannula and inner stylet, is then cocked as shown in the diagram. The needle is passed through the skin into the renal parenchyma, often using ultrasound for real-time guidance. The patient is instructed to hold his or her breath, and then the actuator button is depressed, causing rapid advancement of both the inner stylet and outer cannula to the device's predetermined penetration depth. A tissue core is acquired as the cannula rapidly passes over the stylet. Two or three cores should be acquired to ensure an adequate sample.

The adequacy of the tissue cores can be assessed using low-power microscopic examination. An adequate sample should contain a minimum of 8 to 10 glomeruli. The cores should be transported in normal saline to the pathology laboratory or placed in fixatives if the laboratory is not on site. A renal pathologist then examines the tissue using light microscopy, electron microscopy, and immunofluorescence or immunohistochemistry. Typical routine stains for light microscopy include hematoxylin and eosin, periodic acid–Schiff, Jones' silver methenamine, and trichrome.

COMPLICATIONS

The main complications of a renal biopsy include bleeding, pain, damage/puncture of surrounding structures (liver, spleen, bowel), and arteriovenous fistula formation. Bleeding is by far the most common complication, and it can occur into the urine collecting system, perinephric space, or subcapsular space. Patients should thus be monitored for approximately 4 to 6 hours after the procedure, with vital signs, hemoglobin levels, and urine color noted. Some centers perform a follow-up computed tomography (CT) scan or ultrasound a few hours after the biopsy. In the event of a major bleed, transfusions or therapeutic procedures (e.g., angioembolization or laparotomy) should be performed as needed. In very rare cases, a renal biopsy results in kidney loss or death.

HEMODIALYSIS, PERITONEAL DIALYSIS, AND CONTINUOUS THERAPIES

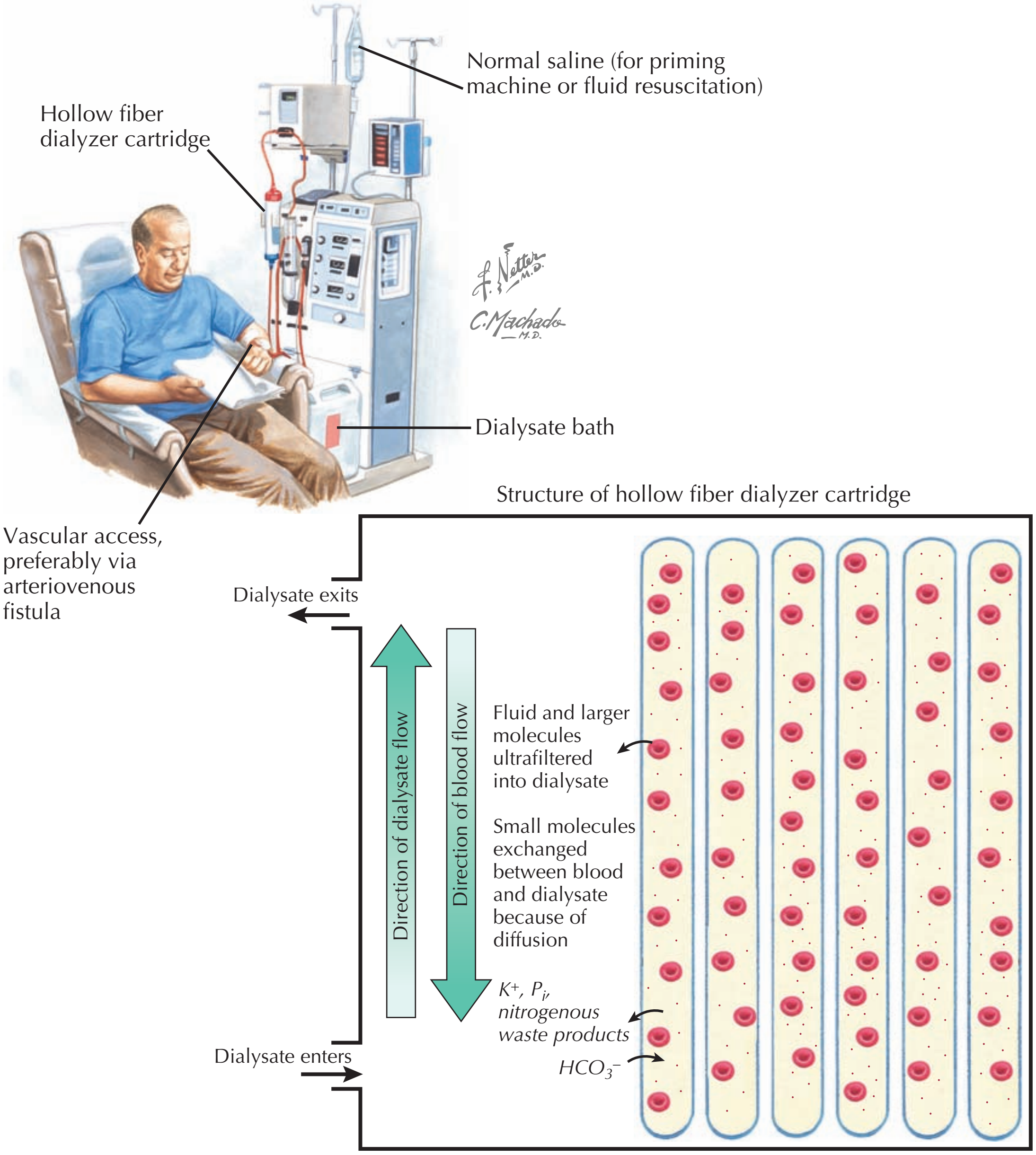
HEMODIALYSIS

Indications

- Metabolic acidosis that is refractory to medical treatment
- Electrolyte abnormalities, such as hyperkalemia, that are refractory to medical treatment
- Intoxication with dialysable drugs (e.g., salicylates, lithium)
- Volume overload that is refractory to diuretics
- Uremia and its complications (encephalopathy, pericarditis, bleeding)

In patients with chronic kidney disease:

- Glomerular filtration rate $<10–15$ mL/min/1.73m^2
- Weight loss, anorexia, loss of appetite
- Any of the sequelae of impaired renal function listed above


Normal saline (for priming machine or fluid resuscitation)
Hollow fiber dialyzer cartridge
F. Netter M.D.
C.Machado M.D.
Dialysate bath
Vascular access, preferably via arteriovenous fistula
Structure of hollow fiber dialyzer cartridge
Dialysate exits
Direction of dialysate flow
Direction of blood flow
Fluid and larger molecules ultrafiltered into dialysate
Small molecules exchanged between blood and dialysate because of diffusion
K+, Pi, nitrogenous waste products
HCO3−
Dialysate enters

When kidney dysfunction is severe enough to cause homeostatic abnormalities that cannot be corrected with diet or medications, dialysis is performed to artificially replace the kidney's major functions. The major goals of dialysis are to support the elimination of nitrogenous waste products, restore fluid and electrolyte homeostasis, and restore normal plasma pH. The major indications are listed in the plate.

PRINCIPLES OF DIALYSIS

Dialysis employs a semipermeable membrane to alter the composition of blood. Blood is located on one side of the membrane, whereas a wash solution, known as the dialysate, is on the opposite side. The objective is for the desirable electrolytes to move from the dialysate to the blood and for the undesirable electrolytes to move in the opposite direction. The movement of fluid and solutes across the membrane depends on two physical forces: diffusion and convection.

In diffusion, solute transport is directly dependent on the concentration gradient of the solute, diffusivity of the solute, permeability of the membrane, and surface area across the membrane. The smaller the molecule, the more rapidly it will diffuse. Molecules continue to move across the membrane until equilibrium is achieved.

In convection, solutes are dragged across a membrane in the solvent that contains them. An analogy would be an ocean wave (the solvent) pushing sea shells (the solute) onto the shore. The solvent carrying these solutes crosses the membrane in a process known as ultrafiltration, which depends on the pressure gradients across the membrane.

Diffusion is more efficient at clearing small molecular weight substances (less than 500 Da), such as electrolytes. In contrast, convection is more efficient at clearing medium molecular weight substances (500 to 5000 Da), such as vitamin B_{12} or drugs (e.g., vancomycin).

Hemodialysis. In hemodialysis, blood leaves the patient and flows through tubing into a dialyzer. The dialyzer contains numerous hollow fibers composed of semipermeable membranes. As blood flows through these fibers, dialysate flows around them in the opposite direction. Molecules are exchanged across the fiber walls. The blood then returns to the patient.

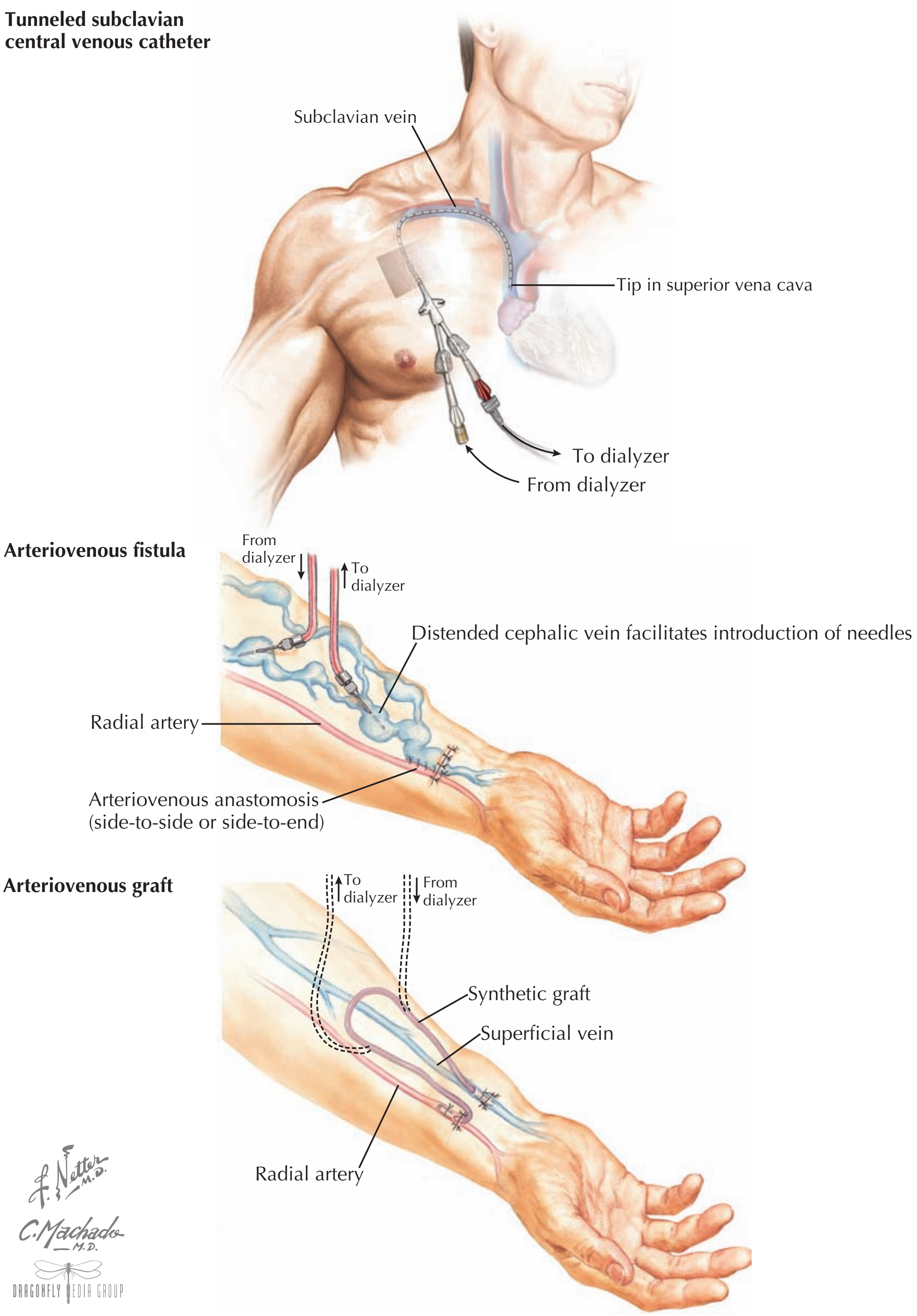
Because blood and dialysate flow in opposite directions, concentration gradients are maintained across the entire length of the dialyzer. As a result, potassium, nitrogenous waste products, phosphorus, and other substances that have accumulated in the blood diffuse into the dialysate. Meanwhile, substances that are concentrated in the dialysate, such as bicarbonate and other electrolytes at specific concentrations, diffuse into the blood to restore desired levels. As diffusion occurs, the hydrostatic pressure in the dialyzer leads to ultrafiltration of fluid and convection of larger solutes.

The patient's vasculature can be accessed using either a central venous catheter (CVC) or a connection between an artery and vein (fistula or graft). A CVC used for dialysis contains two lumens and is inserted into a large central vein. The rapid and substantial amount of flow (up to 400 to 500 mL/min) drawn from these veins allows blood to efficiently exit the vein through one lumen, enter the dialysis circuit, and return to the vein through another lumen. The high blood flow also prevents stasis, which could lead to clotting, and optimizes the exchange of solutes across the membrane. Heparin is often used at intervals to prevent clotting within the dialysis circuit.

The main disadvantage of CVCs is their infection risk. To decrease this risk, catheters are often tunneled, meaning they are passed through a subcutaneous tract

HEMODIALYSIS, PERITONEAL DIALYSIS, AND CONTINUOUS THERAPIES *(Continued)*

VASCULAR ACCESS FOR HEMODIALYSIS


Tunneled subclavian central venous catheter

Arteriovenous fistula

Arteriovenous graft

before being inserted into the central vein. This process lengthens the distance that skin flora must travel before being able to cause a systemic infection.

In addition to the risk of infection, catheters can also clot and kink, and they can incite an inflammatory reaction that leads to venous stenosis. Thus even tunneled CVCs should be considered temporary access routes to be used only while awaiting creation of a more permanent solution, such as an arteriovenous fistula or graft.

An arteriovenous fistula permits the high blood flow of the artery to be shunted into a neighboring vein. After a fistula is surgically created, the vein will dilate and thicken over the course of 6 to 8 weeks, after which dialysis needles can safely be inserted and removed as needed. Fistulas most often join the cephalic vein and radial artery in a side-to-side or end-to-side anastomosis, although many other configurations are possible.

If a patient has diseased peripheral vasculature that would not permit the creation of a fistula, usually because of complications from diabetes mellitus, an artificial graft can be implanted to join the artery and vein. These grafts, often made of polytetrafluoroethylene, can be used for hemodialysis within 1 to 2 weeks of implantation. Their disadvantages, however, are that they do not remain patent for as long as fistulas, and that they are more likely to become stenosed or thrombosed.

Once vascular access has been established, several different hemodialysis schedules can be used. A standard schedule consists of 3- to 4-hour sessions occurring three times per week. Nocturnal hemodialysis, also performed three times per week, consists of 8- to 10-hour sessions (at reduced blood and dialysate flow rates) performed while the patient sleeps. Short daily hemodialysis consists of 2- or 3-hour sessions occurring five to six times per week. At-home dialysis is becoming increasingly common and allows for more flexible schedules compared to in-center hemodialysis.

Peritoneal Dialysis. In peritoneal dialysis, dialysate is instilled into the intraperitoneal space. Blood in the peritoneal capillaries exchanges material with the dialysate using the peritoneal membrane as a natural semipermeable membrane. The dialysate dwells in the peritoneum for 2 to 12 hours and is then removed. Each sequence of instillation, dwelling, and draining is known as a cycle (or exchange).

The dialysate is a sterile solution that contains variable concentrations of glucose. While the dialysate is in the peritoneum, substances such as urea and potassium diffuse from the capillaries into the dialysate, whereas glucose and lactate diffuse in the opposite direction. Fluid ultrafiltration occurs because of the osmotic gradient established by the glucose, resulting in the convective clearance of larger molecules.

The dialysate is instilled into the abdominal cavity through a surgically tunneled catheter (Tenckhoff), which remains in place between sessions. Given the risk of peritonitis with an indwelling catheter, patients must be instructed to perform each exchange using sterile technique.

Several different schedules may be used. In continuous ambulatory peritoneal dialysis (CAPD), approximately four exchanges are performed per day. During each session, 1.5 to 3 L of dialysate dwell in the peritoneal cavity for 6 hours. The patient must manually instill and then drain or remove the dialysate. In automated peritoneal dialysis (APD), 4 to 5 exchanges occur overnight. During each session, 1.5 to 3 L of dialysate dwell in the peritoneal cavity for 2 hours. In this case, a machine performs the exchanges. Continuous cyclic PD (CCPD) is a regimen in which 3 to 4 exchanges are performed automatically overnight,

HEMODIALYSIS, PERITONEAL DIALYSIS, AND CONTINUOUS THERAPIES *(Continued)*

while 1 to 2 long dwell exchanges are performed manually during the day.

Peritoneal dialysis is less efficient than hemodialysis; however, because it is performed daily, patients still attain adequate clearance and generally feel better and have fewer dietary restrictions than with in-center hemodialysis. In addition, the patient can perform peritoneal dialysis at home and with less equipment than required by hemodialysis.

CONTINUOUS THERAPIES

Continuous renal replacement therapy (CRRT) is similar to hemodialysis in some respects; however, sessions are continuous, rather than discrete, and the flow rate is lower (100 to 300 mL/min). CRRT is performed when patients require dialysis but are hemodynamically unstable or have homeostatic abnormalities that cannot be addressed with an individual hemodialysis session. For example, if a patient in renal failure is expected to receive a large volume load (in the form of transfusions or antibiotics), it may be advantageous to receive continuous renal replacement therapy.

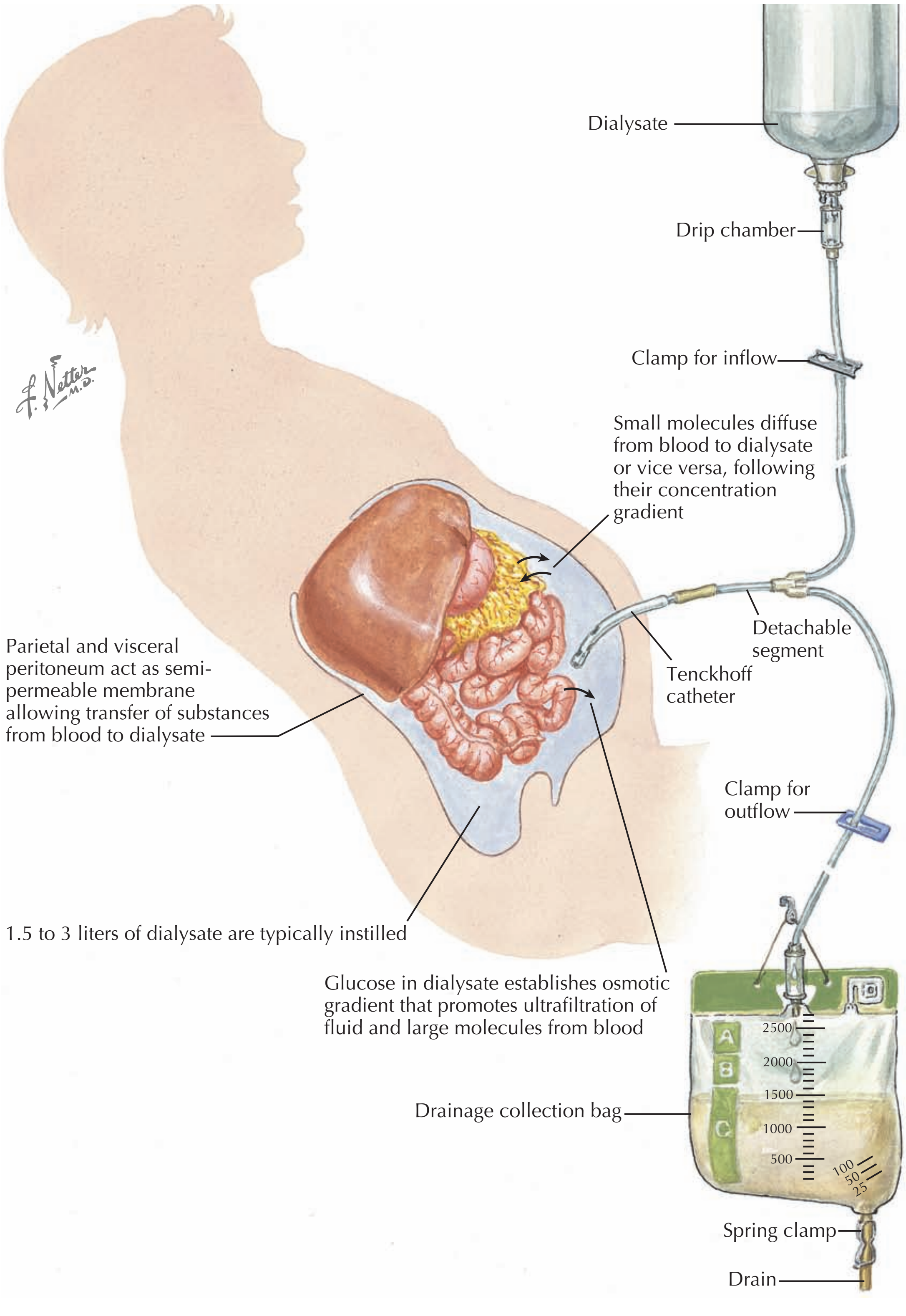
As in hemodialysis, a connection is established between the patient's vasculature and an extracorporeal apparatus. Access is established using a central venous catheter. AV fistulae or grafts cannot be used because the constant presence of needles in these vessels (in contrast to the episodic presence associated with hemodialysis sessions) could lead to damage and infection, which would prevent future use.

CRRT uses the principles of hemodialysis (diffusive clearance) and hemofiltration (convective clearance) either alone or in combination. A variety of different configurations may be used. The most common include:

Slow continuous ultrafiltration (SCUF)—In this modality, fluid is removed from the blood by hemofiltration alone. No dialysate is used. This modality is generally used for fluid-overloaded patients (e.g., congestive heart failure) who are not responsive to diuretics but who have preserved electrolyte balance.

Continuous veno-venous hemofiltration (CVVH)—In this modality, convective clearance is achieved by using hydrostatic pressure to ultrafilter plasma across a membrane, as with SCUF. In this case, however, a replacement fluid is added either before or after the blood enters the filter cartridge; it is similar in content to dialysate and, when mixed with blood, brings its electrolyte composition into a desirable range.

PERITONEAL DIALYSIS


Dialysate
Drip chamber
Clamp for inflow
F. Netter M.D.
Small molecules diffuse from blood to dialysate or vice versa, following their concentration gradient
Detachable segment
Tenckhoff catheter
Parietal and visceral peritoneum act as semipermeable membrane allowing transfer of substances from blood to dialysate
Clamp for outflow
1.5 to 3 liters of dialysate are typically instilled
Glucose in dialysate establishes osmotic gradient that promotes ultrafiltration of fluid and large molecules from blood
A
B
C
2500
2000
1500
1000
500
100
50
25
Drainage collection bag
Spring clamp
Drain

Continuous veno-venous hemodialysis (CVVHD)—CVVHD is similar to hemodialysis as described earlier but is continuous rather than episodic. This modality consists primarily of diffusive clearance of small molecules. Some convective clearance occurs, but to a lesser extent than diffusive clearance.

Continuous veno-venous hemodiafiltration (CVVHDF)—CVVHDF combines both CVVHD and CVVH. In this modality, a replacement solution infuses into the blood either prefiltration or postfiltration. At the same time, a dialysate solution runs countercurrent to the blood in the filter cartridge. This modality removes both small and medium-sized molecules from the blood.

Studies are currently being performed to compare the relative advantages of and indications for CVVH, CVVHD, and CVVHDF.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Extracorporeal shock wave lithotripsy (ESWL) is a noninvasive procedure for the treatment of nephrolithiasis. In this procedure, acoustic shock waves are generated external to the patient and focused on the renal stones, which are fragmented into small pieces that can be spontaneously passed in the urine. The skin and surrounding renal parenchyma receive a much smaller dose of energy and therefore remain largely unharmed.

SHOCKWAVE PHYSICS

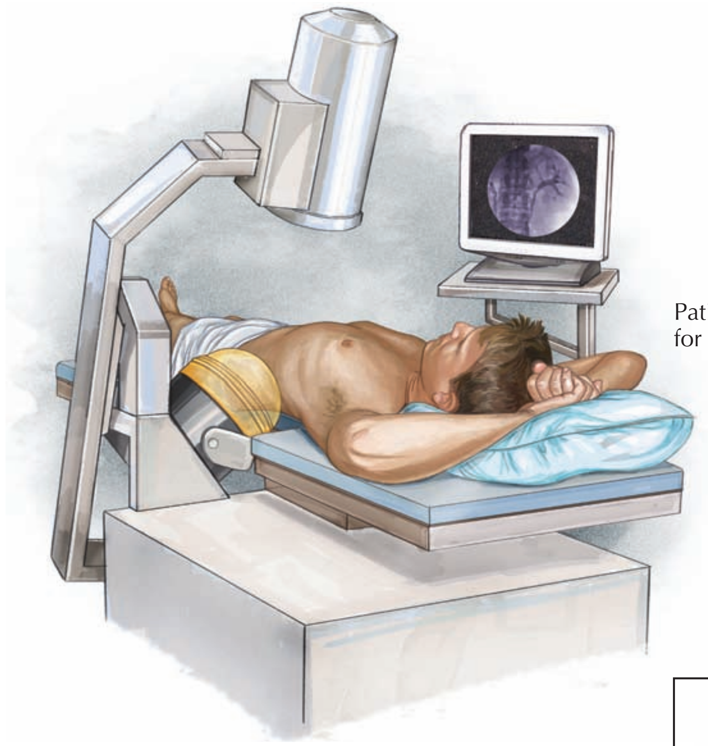
Shockwaves fragment renal stones through multiple mechanisms. A direct effect occurs because of the difference in density between the stones and surrounding fluid. As the waves enter and then exit the stones, they create compressive and then tensile forces that contribute to stone fragmentation. An indirect effect occurs because of the cavitation bubbles that form behind the advancing shock waves, which exert forces on the stones as they collapse.

In current practice, lithotripters create shock waves using electrohydraulic, electromagnetic, or piezoelectric generators. Electrohydraulic lithotripters consist of two underwater electrodes that spark, producing a vaporization bubble that rapidly collapses and generates shock waves. An ellipsoid reflector refocuses these waves so they converge onto the stones. Electromagnetic lithotripters, meanwhile, consist of an electromagnetic coil beneath a metal plate in a water bath. As a charge is passed through a coil, a repulsive magnetic force pushes the plate against the water, generating a shock wave that is focused using an acoustic lens. Finally, piezoelectric lithotripters contain thousands of small piezoelectric crystals arranged under water on a hemispherical surface. These crystals rapidly expand in response to an electrical pulse, generating a shock wave. Because of the configuration of the crystals, no additional focusing is necessary.

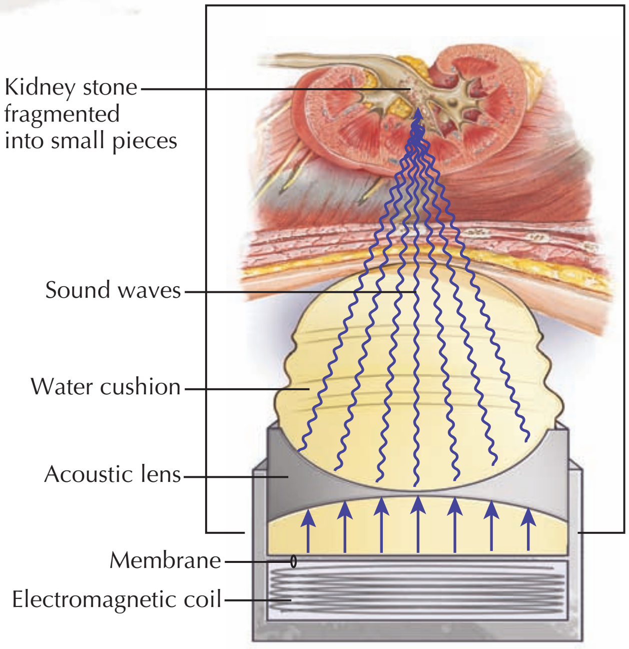
INDICATIONS AND PREOPERATIVE EVALUATION

ESWL is indicated for most uncomplicated upper urinary tract calculi where renal anatomy is normal and the combined diameters of the stones is less than 2 cm. ESWL is also considered an appropriate option for the management of stones anywhere in the ureter, with the exception of middle and lower ureteral stones in women of childbearing age. Of note, ESWL is less effective for “hard” stones composed of calcium oxalate monohydrate, calcium phosphate, or cystine. In addition, certain factors may lower the likelihood of fragment passage, such as lower pole calculi, long and narrow renal infundibula, narrow infundibulopelvic angles, and severe hydronephrosis.

Absolute contraindications to ESWL include pregnancy, severe skeletal malformations (because of altered anatomic relationships), significant coagulopathy, urinary tract infection, and large abdominal aortic aneurysm (because of possible rupture). Relative contraindications include obesity, which diminishes efficacy; cardiac pacemakers, due to concerns over inducing arrhythmias; renal artery aneurysms and chronic pancreatitis, which may be worsened by the procedure; and uncontrolled hypertension, due to an increased bleeding risk.



Patient positioning for lithotripsy



PROCEDURE

Most patients are positioned supine on the lithotripter bed; however, those with stones in anteriorly located kidneys, medial portions of a horseshoe kidney, or transplanted kidneys should be positioned prone to reduce the skin-to-stone distance and remove skeletal structures from the shock wave path. Once the patient is positioned, the stones are localized using fluoroscopy and, in some cases, ultrasound.

During lithotripsy, the body must be coupled with the shock wave source. This process eliminates the transition between ambient air and the patient’s skin, which would otherwise attenuate the shock wave and cause complications such as ecchymoses and skin breakdown. Because soft tissue has an acoustical impedance similar to that of water, coupling can be achieved either by submerging the patient in a water bath, as in earlier systems, or by applying a water cushion with a silicone membrane directly to the patient’s skin.

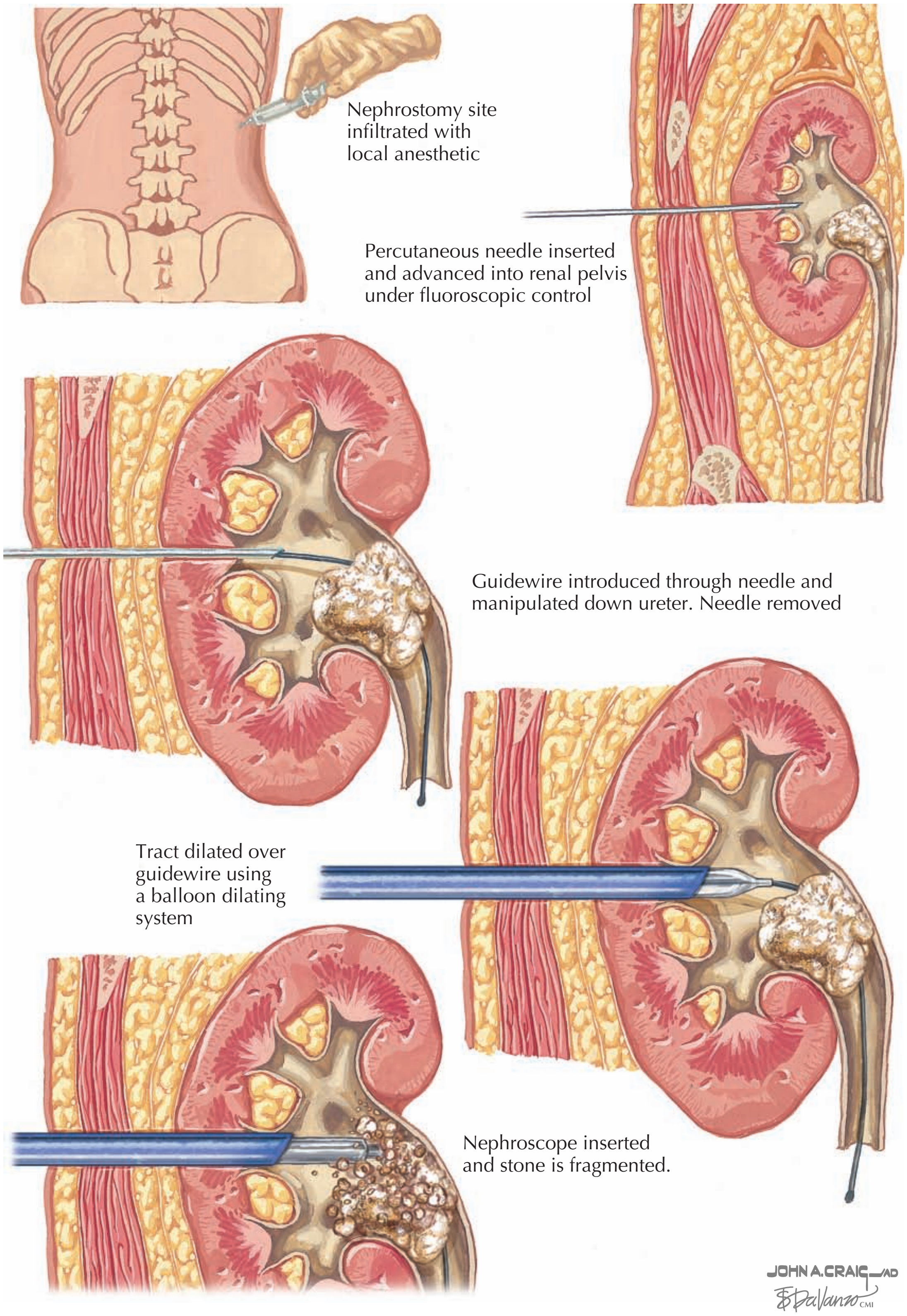
The number of shock waves applied to the stones will impact the degree of fragmentation. Each manufacturer determines a machine-specific dosage that should not be exceeded.

POSTOPERATIVE CARE AND COMPLICATIONS

After lithotripsy, patients are encouraged to ambulate and to increase fluid intake to promote stone passage. Postprocedural gross hematuria is common and transient. A mild to moderate degree of abdominal or flank pain is also common; however, severe and persistent pain suggests complications such as hematoma or impaction of stone fragments, which should prompt evaluation with CT scan.

In the absence of a more acute indication, follow-up is typically performed at 2 weeks and includes repeat imaging to assess the success of stone fragmentation and passage. If necessary, residual stones may be treated with a repeat ESWL procedure or other techniques.

PERCUTANEOUS NEPHROLITHOTOMY: CREATION OF ACCESS TRACT


Nephrostomy site infiltrated with local anesthetic
Percutaneous needle inserted and advanced into renal pelvis under fluoroscopic control
Guidewire introduced through needle and manipulated down ureter. Needle removed
Tract dilated over guidewire using a balloon dilating system
Nephroscope inserted and stone is fragmented.
JOHN A.CRAIG AD
DaVanzo CMI

PERCUTANEOUS NEPHROLITHOTOMY

Percutaneous nephrolithotomy (PCNL) is a minimally invasive procedure for the treatment of kidney stones. In this procedure, a surgical access tract is established between the skin and the renal collecting system. The tract is typically created under fluoroscopic guidance, with needle puncture followed by tract dilation.

Although more invasive than extracorporeal shock wave lithotripsy (ESWL, see Plate 10-12) and ureteroscopic laser lithotripsy (URSLL, see Plate 10-34), PCNL is highly effective for large kidney stones and patients with more complex stone disease. Before the introduction of PCNL, these challenging patients were managed almost exclusively with open or laparoscopic surgery, which is far more invasive, requires longer convalescence, and has higher rates of morbidity, mortality, and stone recurrence. In contemporary practice, however, open surgery is now performed only in special situations, such as morbid obesity, numerous stenotic infundibulae, ectopic kidneys without safe percutaneous access, extremely complex stones that would require numerous access tracts, and coagulopathies.

INDICATIONS

The factors that determine the difficulty, and thus appropriateness, of PCNL include the degree of hydronephrosis, total stone burden (i.e., surface area), stone composition, number of calyces involved, presence or absence of infundibular stenosis, and presence or absence of anatomic abnormalities (e.g., horseshoe and pelvic kidneys).

The presence of hydronephrosis makes it easier to maneuver rigid instruments within the collecting system, and therefore PCNL is preferred over other techniques in patients with hydronephrotic kidneys.

A large stone burden is a common indication for PCNL because large fragments can easily be extracted via single or multiple percutaneous tracts. In contrast, ESWL requires patients to pass these fragments spontaneously, and URSLL requires removal of these stones through the ureter.

Stone composition is an important factor because hard stones, such as those composed of cystine or calcium oxalate monohydrate, often do not respond to ESWL and are more difficult to fragment with URSLL. Thus PCNL is usually preferable.

The more calyces that contain stones, the lower the success rate of ESWL and URSLL, since it is difficult to treat stones in multiple locations with these modalities. Thus PCNL is preferred because of its higher stone-free rate and reduced need for ancillary procedures.

Unusual collecting system anatomy, in particular infundibular stenosis, often precludes successful elimination of stone fragments following ESWL and URSLL, again making PCNL the better choice.

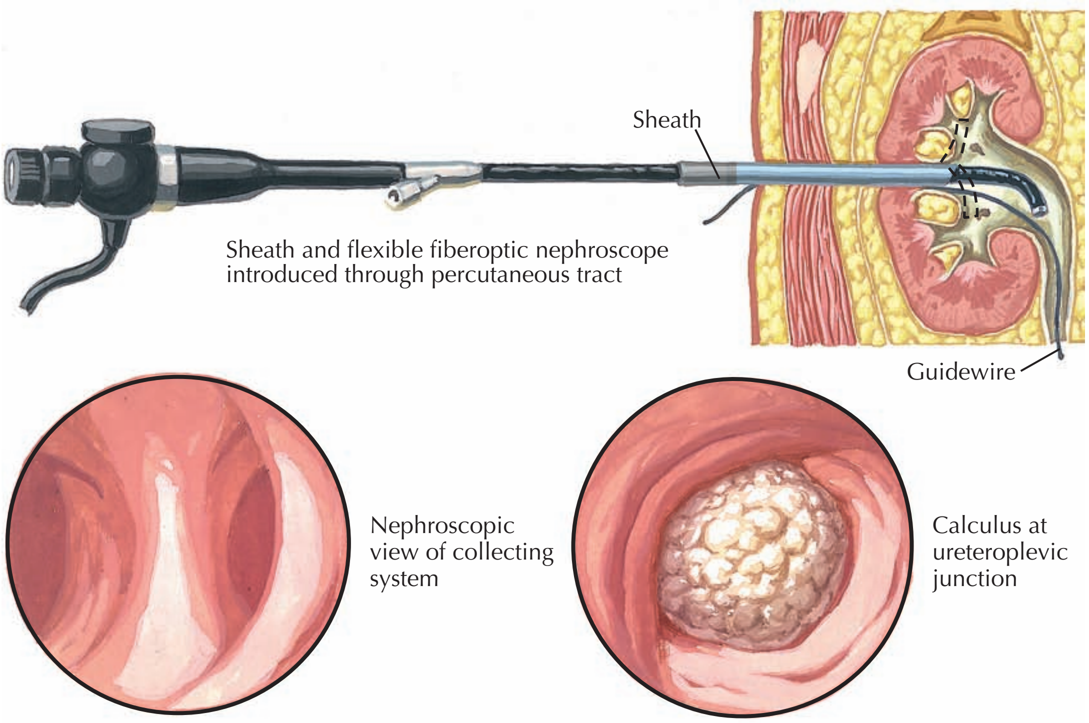
Finally, congenitally abnormal kidneys, such as horseshoe kidneys and pelvic kidneys, usually have anteriorly located ureteropelvic junctions, which can make spontaneous passage of stones after ESWL and ureteral extraction of stones during URSLL very challenging. The unusual position of the ureteropelvic junction, along with the collecting system dilation that often accompanies these ectopic kidneys, makes PCNL the preferred choice.

TECHNIQUE

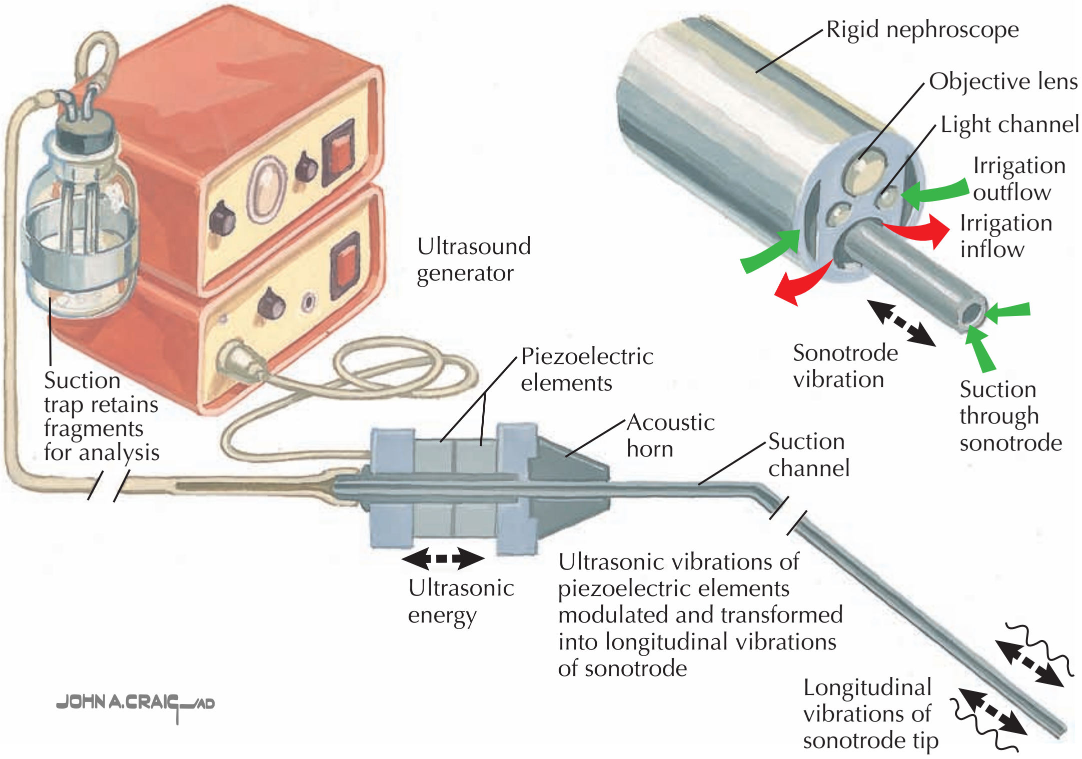
Patients scheduled for PCNL must have a documented sterile urine culture because PCNL in the setting of

Nephroscope and Sonotrode

Nephroscope


Sheath
Sheath and flexible fiberoptic nephroscope introduced through percutaneous tract
Guidewire
Nephroscopic view of collecting system
Calculus at ureteroplevic junction

Sonotrode


Rigid nephroscope
Objective lens
Light channel
Irrigation outflow
Irrigation inflow
Ultrasound generator
Suction trap retains fragments for analysis
Piezoelectric elements
Sonotrode vibration
Suction through sonotrode
Acoustic horn
Suction channel
Ultrasonic energy
Ultrasonic vibrations of piezoelectric elements modulated and transformed into longitudinal vibrations of sonotrode
Longitudinal vibrations of sonotrode tip
JOHN A.CRAIG—AD

PERCUTANEOUS NEPHROLITHOTOMY *(Continued)*

urinary tract infection can lead to urosepsis. The procedure is performed under general anesthesia, and the patient is typically prone. More recently, however, techniques have been described in which PCNL is performed in the supine and flank positions.

Imaging is typically performed using fluoroscopy. Before access is attempted, most surgeons deploy a ureteral catheter into the ipsilateral ureter for retrograde injection of contrast or irrigant, which facilitates visualization of the renal collecting system.

The key to successful PCNL is the site chosen for entry into the collecting system. Lower pole access is excellent for stones that are in the lower pole or renal pelvis, but it offers limited access to the other calyces and is thus not well suited for staghorn stones, complex stones, or stones in multiple calyces. Lower pole access, however, is associated with a smaller risk of entering the pleural space. In contrast, upper pole access provides the surgeon the best access to the entire collecting system, but it is associated with a modest risk of entering the pleural space.

In most situations, a posterior calyx should be chosen for access because its orientation permits entry into the renal pelvis and other calyces from a typical posterolateral approach. If the patient has a solitary stone, however, it generally makes most sense to enter the calyx that contains the stone, even if it is in an anterior position.

Generally, the posterior upper pole calyx permits maximum stone extraction from a single access tract.

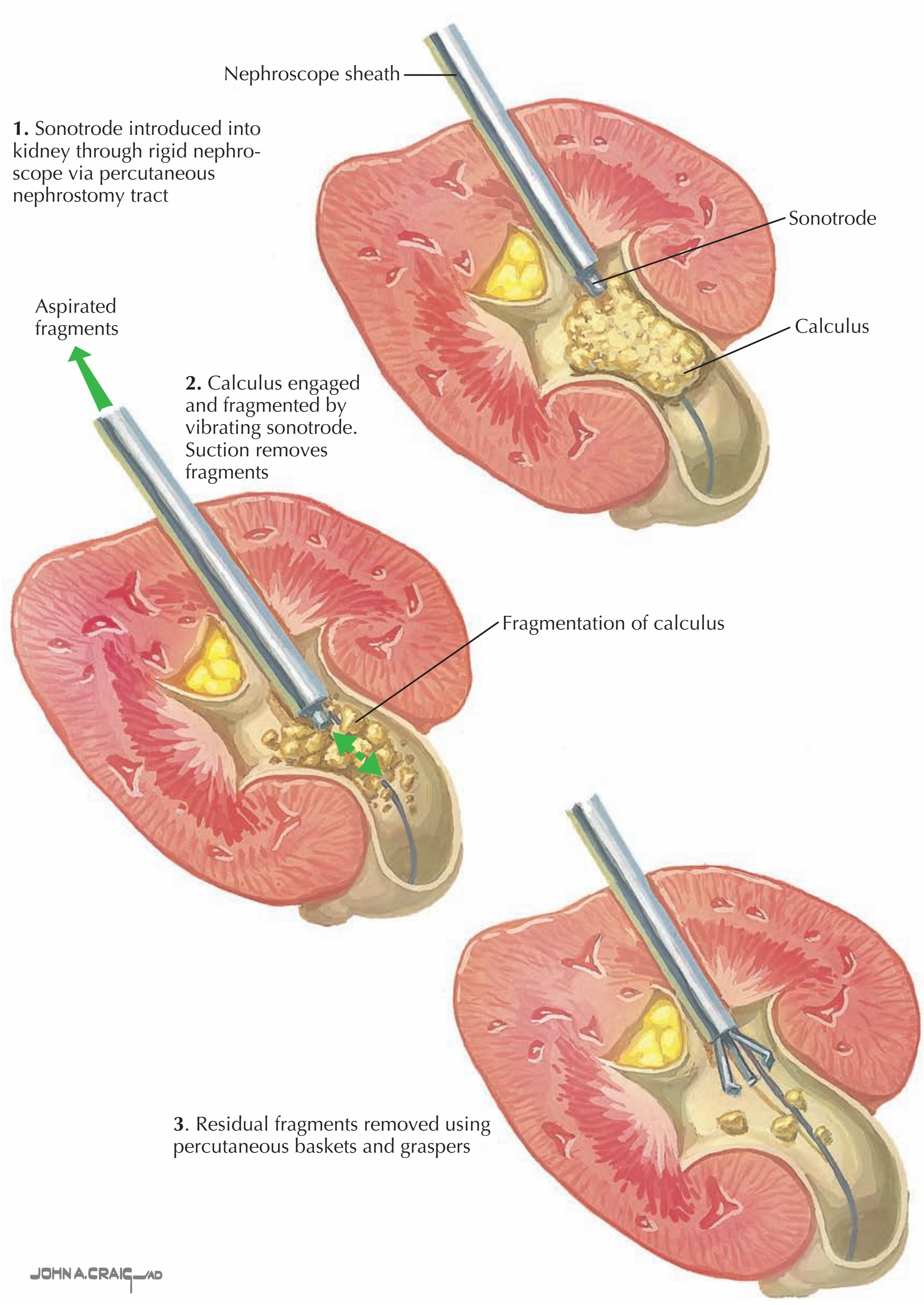
Once a calyx has been selected, an important decision must then be made between intercostal or subcostal placement of the access tract. Subcostal tracts are preferable because they minimize the chance of pleural injury, which could result in pneumothorax, hemothorax, or hydrothorax. Such tracts, however, may place a significant amount of torque on the kidney, potentially causing damage.

In general, the fear of intercostal tracts is unfounded as long as care is taken to assure that the sheath remains inside the collecting system. Under these conditions, most small pleural transgressions will not result in complications. In contrast, a pleural transgression that is associated with a sheath outside of the collecting system can result in the passage of irrigant, air, or blood into the pleural space. A postprocedure chest radiograph or chest fluoroscopy is recommended to permit early diagnosis of pulmonary complications, so that a chest tube can be placed if necessary.

Once the access site has been selected, the procedure is initiated with the percutaneous deployment of a needle into the kidney. Contrast material is injected through the needle to confirm appropriate positioning, and a wire can then be placed into the kidney through the needle. Using this wire, a tract is developed between the skin and the collecting system.

In the past, tract dilation was accomplished using either metallic telescoping dilators (the Alken system) or Teflon-coated graduated dilators (the Amplatz system). At present, however, most centers use balloon-dilating systems. These offer single-step dilation that causes less bleeding than previous systems because of the application of radial, rather than shear, force. In balloon dilation, a deflated balloon with a hollow core is passed over the previously deployed wire. The balloon contains radiopaque markers at its proximal and distal edges to ensure proper positioning. The balloon is then inflated under pressure. Once the balloon is turgid, a plastic sheath can be deployed over the balloon. The balloon is then deflated and removed, while leaving the sheath in position for continued renal access.

ULTRASONIC LITHOTRIPSY OF LARGE STONES


Nephroscope sheath
1. Sonotrode introduced into kidney through rigid nephroscope via percutaneous nephrostomy tract
Sonotrode
Calculus
Aspirated fragments
2. Calculus engaged and fragmented by vibrating sonotrode. Suction removes fragments
Fragmentation of calculus
3. Residual fragments removed using percutaneous baskets and graspers
JOHN A.CRAIG_AD

PERCUTANEOUS NEPHROLITHOTOMY *(Continued)*

Balloon dilators, however, are not always successful. In some collecting systems, the balloon may not reach the target because of the lead length problem; specifically, the tip of the balloon-dilating catheter may hit the stone or be within a small calyx, but the body of the balloon may not reach the collecting system. In addition, patients with a history of prior renal surgery may have a perirenal scar that prevents full balloon inflation, leading to a “waist” in the tract. Finally some obese patients may have so much subcutaneous fat that the balloon is not long enough to reach the collecting system.

Multiple access tracts may be required in patients with large or complex stones, such as staghorn calculi, or with duplicated collecting systems. In some cases, the need for multiple access tracts can be obviated using the stone push technique, in which a trocar needle is placed directly onto a stone located in an inaccessible calyx. The needle is then used to push the stone into the renal pelvis, from which it can be more easily extracted.

Once access into the collecting system has been established, the stones are removed. As most access tracts are 30 Fr in diameter (10 mm), stones up to 10 mm can be directly grasped and extracted using a flexible nephroscope. Larger stones require fragmentation (lithotripsy), which can be accomplished using several different devices. The most common remains percutaneous ultrasonic lithotripsy, in which a probe with a vibrating tip (known as a sonotrode) produces ultrasonic energy that fragments the stones. Because the probe is hollow, it can be attached to suction, such that stone fragments are extracted as they are created. Pneumatic lithotripsy (hammer-like effect) has also been used for stone fragmentation alone or in conjunction with ultrasonic stone ablation. More recently, some authors have described the use of a holmium laser to fragment stones. Each of these modalities can effectively ablate stones of any composition; however, ultrasonic lithotripsy remains the gold standard.

After all stones have been extracted, the kidney is drained to facilitate healing. A nephrostomy tube can be deployed, but a more recent development is the “tubeless PCNL,” in which an indwelling ureteral stent is deployed and no percutaneous tract is left. Although not truly “tubeless,” these stents do not appear to have higher bleeding rates than conventional nephrostomy drains, even despite the lack of a large tube to tamponade the access tract.

COMPLICATIONS

The major complications associated with PCNL are hemorrhagic. Occasionally, PCNL procedures need to be aborted before complete stone ablation if bleeding prohibits adequate stone visualization. Bleeding is most commonly venous in origin, and it can be controlled by inflation of the balloon to achieve a tamponade effect. Bright red blood is a sign of arterial bleeding and should be treated with immediate tamponade followed by intravascular embolization as needed.

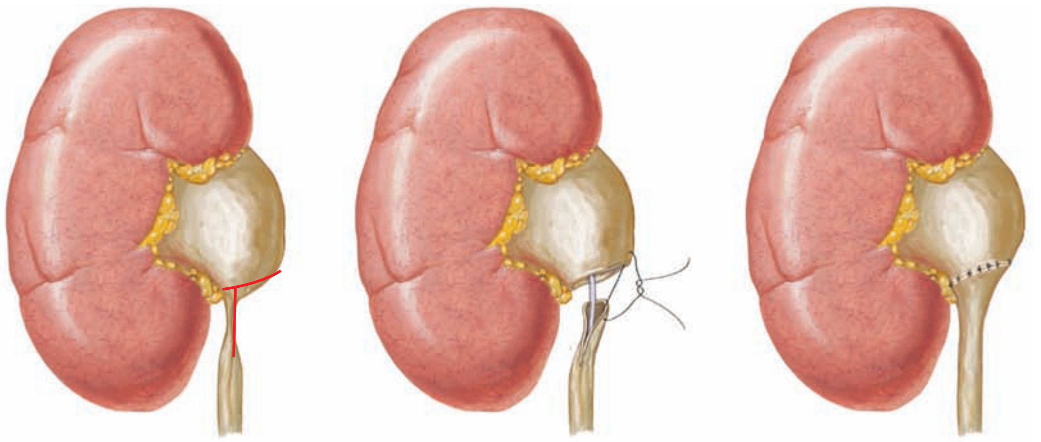
Another complication of PCNL is perforation of the renal collecting system, which can result in ascites. In severe cases, the intraperitoneal fluid can inhibit diaphragmatic contraction and may necessitate prolonged intubation.

Finally, residual stones are common after PCNL procedures. Some surgeons perform a “second look” procedure 1 to 2 days after the primary procedure using the same access tract. Smaller residual fragments can be treated with active surveillance, ESWL, or ureteroscopy.

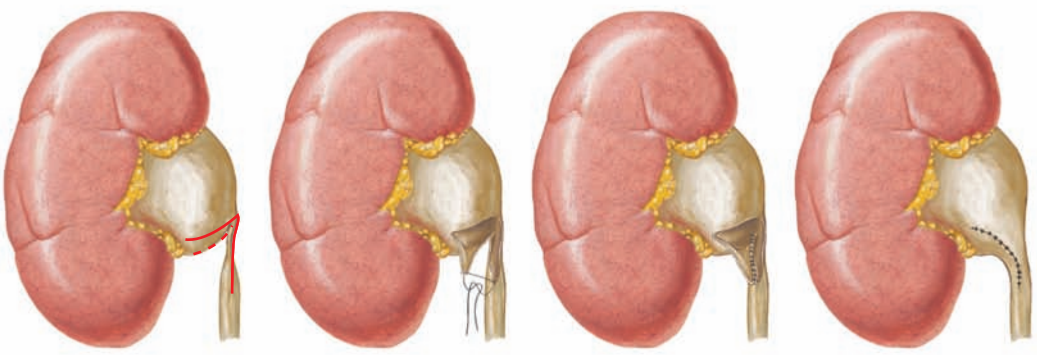
PYELOPLASTY AND ENDOPYELOTOMY

A pyeloplasty or endopyelotomy may be performed to treat an obstruction of the ureteropelvic junction (UPJ, see Plate 6-6). A pyeloplasty consists of surgical reconstruction of the UPJ, whereas endopyelotomy consists of intraluminal, endoscopic incision of the obstruction.

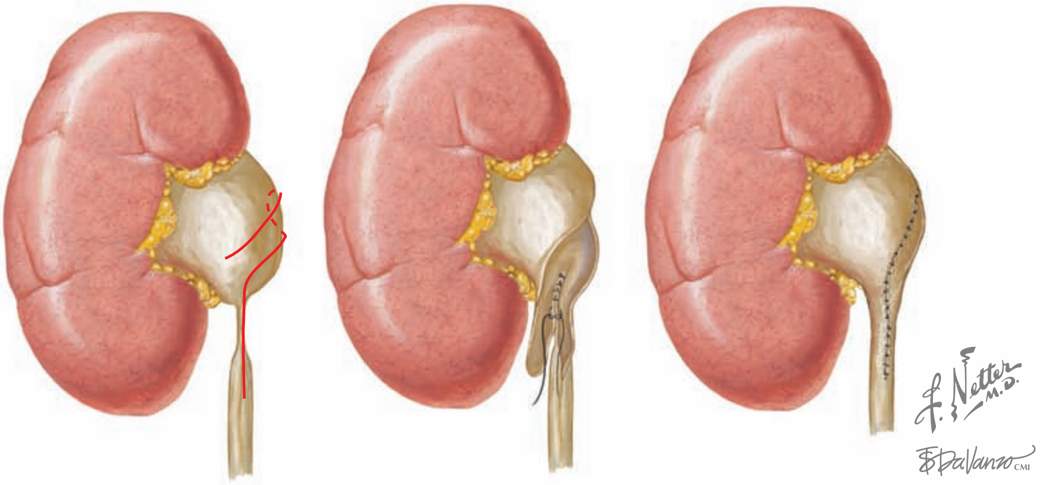
Standard dismembered pyeloplasty



Y-V plasty



Spiral flap



PYELOPLASTY

Pyeloplasty remains the gold standard and may be performed using either open or laparoscopic technique. It is especially appropriate for patients with large stone burdens, strictures more than 2 cm long, marked renal pelvis dilation, or radiographic evidence of a crossing vessel.

An open pyeloplasty is typically performed from a retroperitoneal approach (see Plate 10-19), with an incision carried from the tip of the eleventh rib toward the umbilicus. A laparoscopic pyeloplasty, with or without robot assistance, is most often performed transperitoneally, using three or four abdominal trocars.

Once the renal fascia has been entered and the hilum accessed, the UPJ may be reconstructed using various techniques. The most common is the Anderson-Hynes dismembered pyeloplasty. The proximal part of the UPJ is transected, the UPJ and proximal ureter are spatulated laterally, and reanastomosis is performed. The dismembered technique not only treats the UPJ obstruction but also permits transposition of crossing vessels. In addition, redundant renal pelvic tissue may be excised.

In certain situations, other reconstruction techniques may be employed. In the case of a high insertion of the ureter, either a dismembered or a Foley Y-V plasty may be performed. In the latter, a Y-shaped incision is made in the UPJ. The top of the "Y" is made in the dependent aspect of the renal pelvis, while the stem of the "Y" is carried across the inferior aspect of the UPJ. The incision is then closed as a simple V-flap.

In patients with long, atretic UPJ segments, a renal pelvis spiral flap repair may be required. An elliptical incision is made on the anterior aspect of the renal pelvis and UPJ. The apex of the flap, originally from the renal pelvis, is rotated 180 degrees inferomedially and now constitutes the anterior UPJ. To prevent flap ischemia, the flap length to width ratio should not exceed 3:1.

In cases of repeat pyeloplasty, or when a patient has a very small intrarenal pelvis, ureterocalycostomy is performed. A lower pole calyx is exposed and anastomosed end-to-end to the spatulated proximal ureter.

Additional repairs and flaps have been described using both the renal pelvis and the renal capsule, but these are rarely indicated.

ENDOPYELOTOMY

An endopyelotomy begins with direct visualization of the obstruction from either from a retrograde approach (ureteroscopy, see page 10-33) or anterograde approach (nephroscopy, see Plates 10-13 and 10-14). A safety wire is advanced across the stricture, which is then incised using a knife, laser, or other device. The incision is created in a lateral direction, so as to minimize injury to crossing vessels, and should extend through the ureteral mucosa and muscle until periureteral fat is seen. In the case of a high insertion of the ureter into the renal pelvis, an anterior or posterior incision may be required to allow proper marsupialization of the proximal ureter into the renal pelvis.

A ureteral stent or percutaneous nephroureteral stent is placed to facilitate postoperative drainage and can be removed after 4 to 6 weeks. If injury to a crossing vessel is suggested by intraoperative hemorrhage or postoperative hemodynamic instability, the patient should undergo emergent angiographic evaluation and possible embolization.

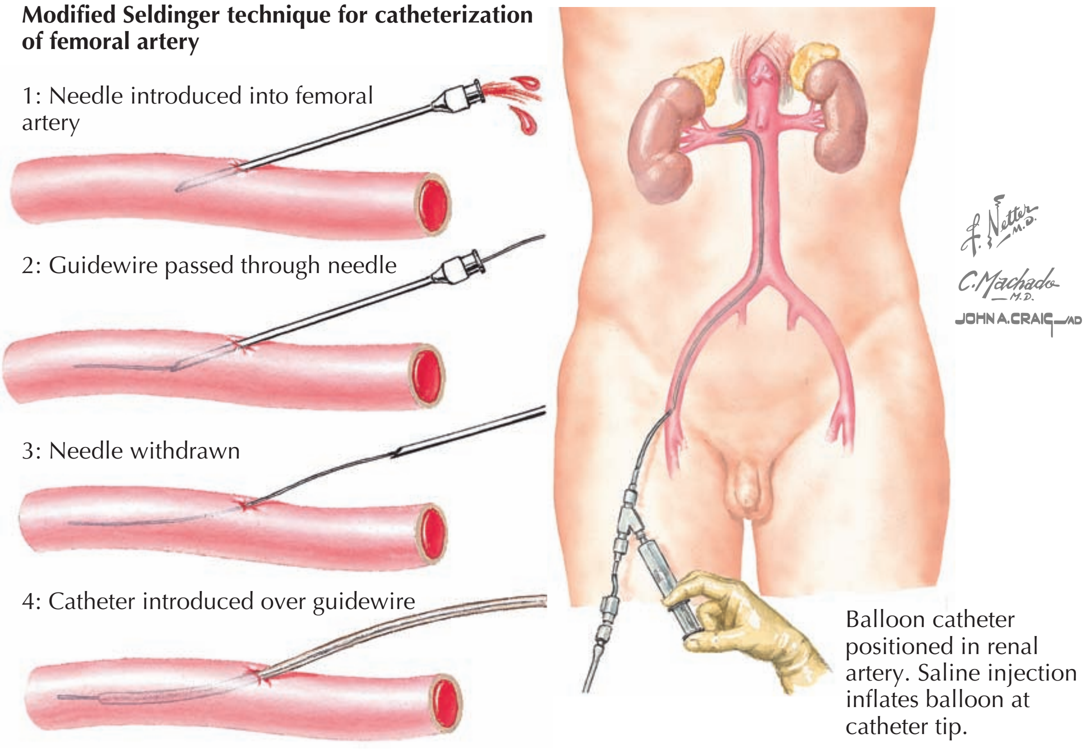
FOLLOW-UP

One month after the procedure, an ultrasound of the kidneys and bladder should be performed. Three months after the procedure, after the stents have been removed, diuretic renography should be performed to confirm the production and unobstructed flow of urine through the affected upper tract.

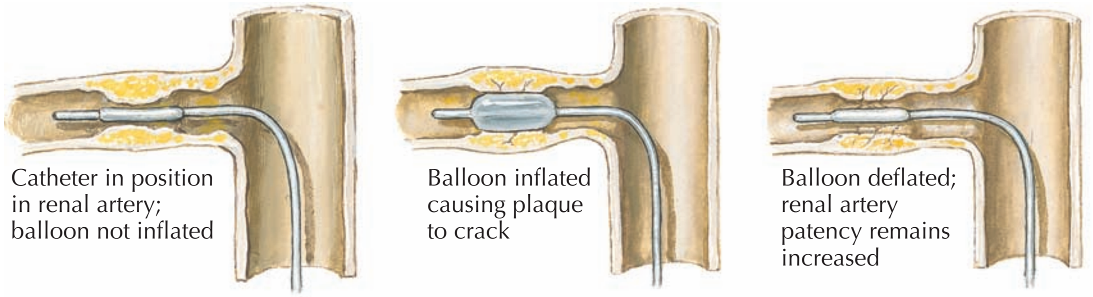
Open pyeloplasty has a long-term success rate of 95%, with comparable rates reported in the laparoscopic and nascent robotic literature. Endoscopic repair appears to be less successful, with failure occurring in up to one third of cases.

ENDOVASCULAR THERAPIES FOR RENAL ARTERY STENOSIS

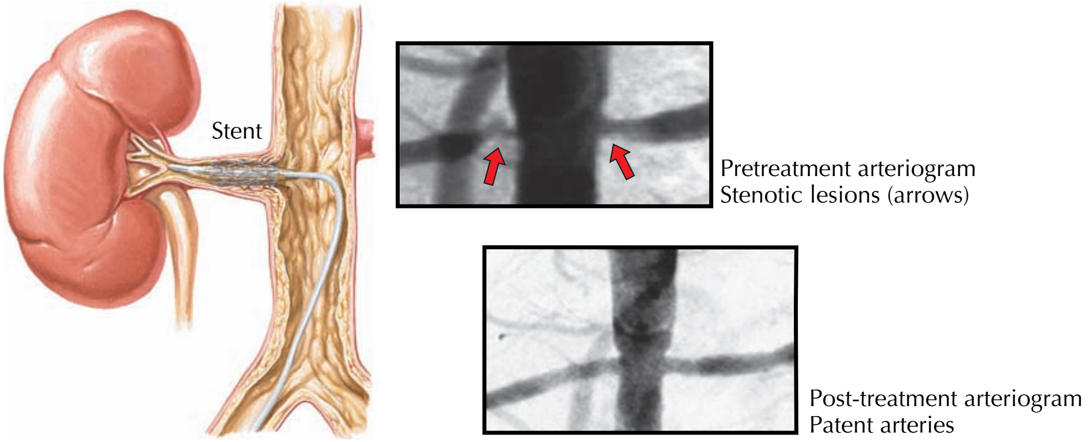
Modified Seldinger technique for catheterization of femoral artery


1: Needle introduced into femoral artery
2: Guidewire passed through needle
3: Needle withdrawn
4: Catheter introduced over guidewire
Balloon catheter positioned in renal artery. Saline injection inflates balloon at catheter tip.
F. Netter M.D.
C. Machado M.D.
JOHN A.CRAIG AD

Balloon angioplasty of atherosclerotic lesion in renal artery


Catheter in position in renal artery; balloon not inflated
Balloon inflated causing plaque to crack
Balloon deflated; renal artery patency remains increased

Stenting of atherosclerotic lesion in renal artery


Stent
Pretreatment arteriogram
Stenotic lesions (arrows)
Post-treatment arteriogram
Patent arteries

RENAL REVASCULARIZATION

Renal artery stenosis (RAS) is defined as an anatomic narrowing of the main renal artery or its segmental branches, which can lead to secondary renovascular hypertension (RVH) and renal failure if sufficiently advanced. The pathophysiology and diagnosis of this lesion are demonstrated in Plates 4-36 and 4-37. Briefly, the major causes are atherosclerosis, which accounts for about 90% of cases, and fibromuscular dysplasia (FMD), which accounts for most of the remainder. Atherosclerosis, which tends to occur in older individuals with classic risk factors, involves the intimal layer of the artery and develops circumferentially to occlude a progressive fraction of the vessel lumen. FMD, in contrast, causes collagenous dysplasia of either the intimal or medial arterial layers.

INDICATIONS AND EVALUATIONS

The initial management of RVH secondary to RAS is with antihypertensive medications, especially ACE inhibitors. The need for surgical intervention depends on the patient's response to antihypertensive medications and the degree (if any) of renal insufficiency. Renal revascularization may be considered if blood pressure is refractory to treatment with multiple agents, or if patients have bilateral stenosis or stenosis of a solitary kidney. In the latter group, revascularization offers the most benefit if there is no intrinsic renal disease and renal function is either intact or only mildly impaired. The resistive index, measured on ultrasound, provides some indication of the degree of renal parenchymal fibrosis, and it has been shown to predict the degree of benefit following intervention.

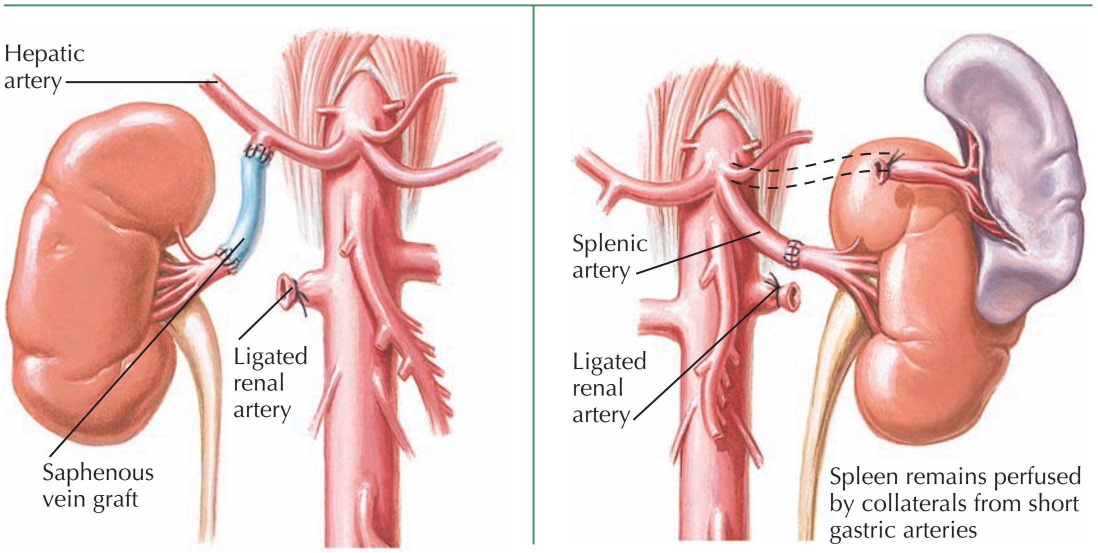
When revascularization is being considered, preoperative assessment depends on the cause of the vascular lesion. Patients with FMD are generally young and in otherwise good health. Patients with atherosclerosis, in contrast, are likely to have disease elsewhere in the vasculature and are thus at increased risk for postoperative myocardial infarction and/or cerebrovascular accident. Therefore, such patients should undergo thorough preoperative evaluation, which may include cardiac stress testing and/or carotid ultrasound.

PROCEDURE

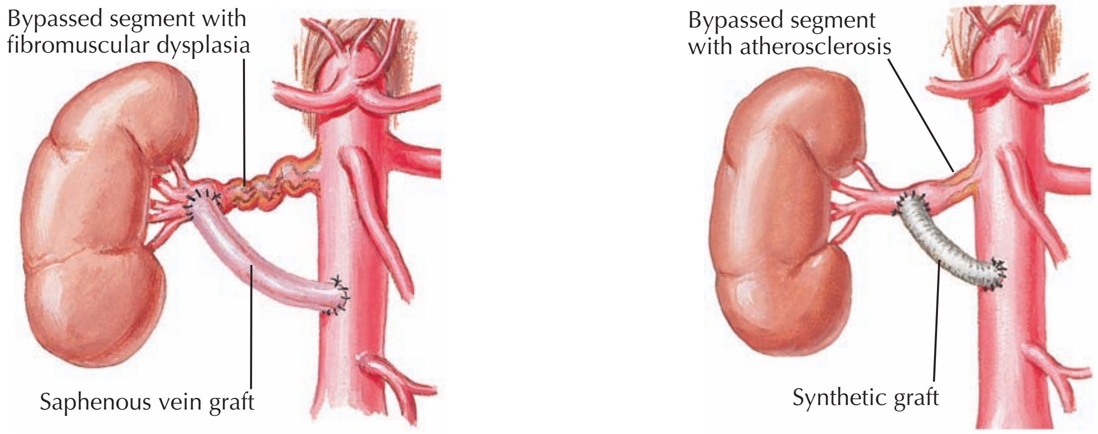
Endovascular repair has become the preferred method for renal revascularization. Open surgical repair, in contrast, is typically reserved for patients who have failed endovascular repair, who have comorbidities such as aortic or renal artery aneurysms, or who have large and complex lesions.

Endovascular revascularization consists of percutaneous dilation of the renal artery (often termed percutaneous transluminal angioplasty, or PTA). The femoral or radial artery is catheterized using the classic or modified Seldinger technique. Under fluoroscopic guidance, with occasional injections of contrast material to opacify the vasculature, a flexible guidewire is advanced across the stenotic segment of the renal artery. A balloon catheter is then selected that is approximately equal to the diameter of the nonstenotic portion of the renal artery. The balloon is placed over the wire to the level of the lesion and then inflated to a high pressure. In patients with atherosclerosis, the inflated balloon fractures the plaque, whereas in patients with FMD, the balloon

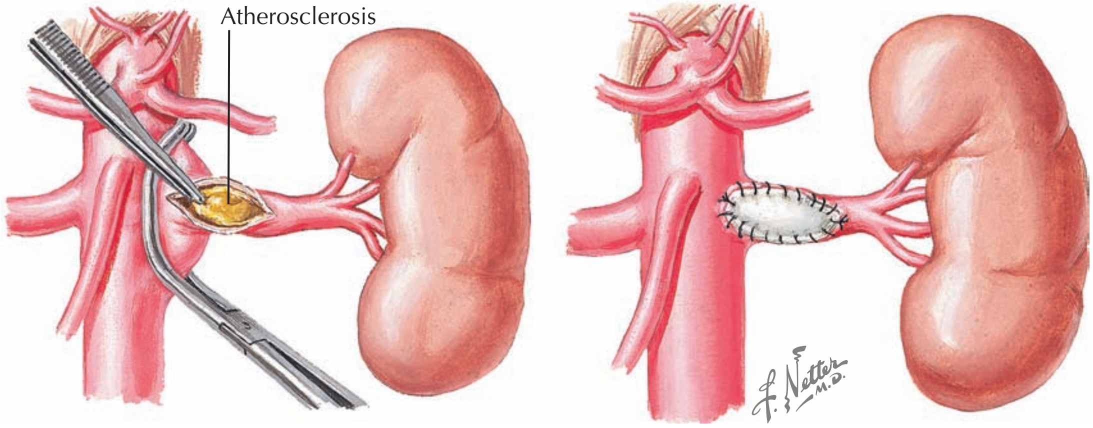
SURGICAL THERAPIES FOR RENAL ARTERY STENOSIS


Hepatorenal bypass **Splenorenal bypass**

Aortorenal bypass


Bypassed segment with fibromuscular dysplasia
Saphenous vein graft
Bypassed segment with atherosclerosis
Synthetic graft

Endarterectomy with patch graft closure



RENAL REVASCULARIZATION

(Continued)

stretches the vessel wall. In either case, perfusion to the kidney is markedly improved. A postdilation angiogram is performed to assess the results and determine the presence of any complications, such as injury to the vessel wall. An adjunct to PTA is the deployment of an endovascular stent, which is an expandable, metallic mesh sheath that helps maintain vessel patency. Stents are especially useful in the treatment of atherosclerotic stenoses, which tend to be rigid and may recoil after balloon dilation.

Surgical revascularization consists of bypass of the stenotic lesion or, less commonly, removal of the obstructing plaque (endarterectomy). Aortorenal bypass is often performed with an autologous graft, such as the saphenous vein. If an autologous graft is not available, a synthetic polytetrafluoroethylene (PTFE) or Dacron graft may be used instead. In patients with severe abdominal aortic disease, in whom aortorenal bypass would be challenging or even dangerous, alternatives include splenorenal or hepatorenal bypass. If both the abdominal aorta and celiac artery have severe stenosis, the lower thoracic aorta may sometimes be used instead. Simultaneous renal revascularization and replacement of the abdominal aorta should not be attempted unless there is another indication for aortic replacement, such as a large aneurysm.

Following either endovascular or surgical treatment, success is defined as elimination of the stenotic lesion on postprocedure angiogram or a postoperative blood pressure of less than 140/90. Many patients show improvements in blood pressure but do not become completely normotensive. The cure rate is greater among patients with FMD than among patients with atherosclerosis, in part because the latter group is more likely to have concomitant essential hypertension.

COMPLICATIONS

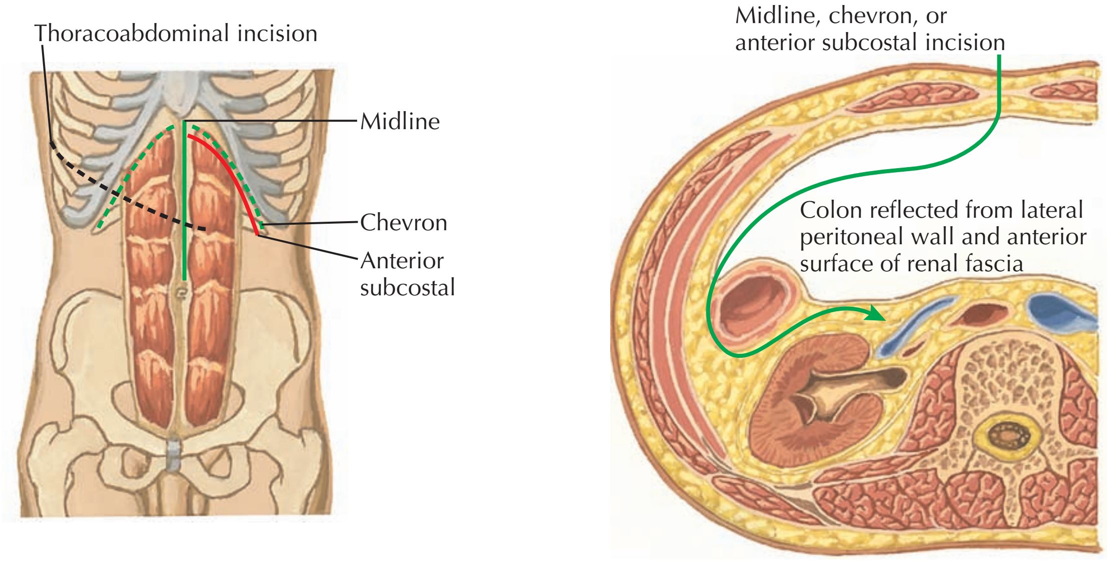
After endovascular repair, patients may experience acute tubular necrosis resulting from the contrast administered during the procedure. To reduce the probability of this complication, patients should receive adequate hydration both before and after the procedure. In addition, all other potentially nephrotoxic medications should be held. Other complications of endovascular repair include hematoma formation near the puncture site, thrombosis of the renal artery secondary to balloon trauma or to inadequate anticoagulation following stent deployment, and restenosis of the repaired lesion. The most serious complication is perforation of the renal artery, which is typically noted during the procedure. In this case, the balloon should be reinflated to tamponade the artery. Emergency open repair may be necessary if bleeding is persistent.

After surgical revascularization, complications include persistent stenosis, graft thrombosis, and restenosis of the repaired lesion. Mortality rates are very low among patients with FMD, owing to their young age and generally good health, but range from 2% to 6% among patients with atherosclerosis.

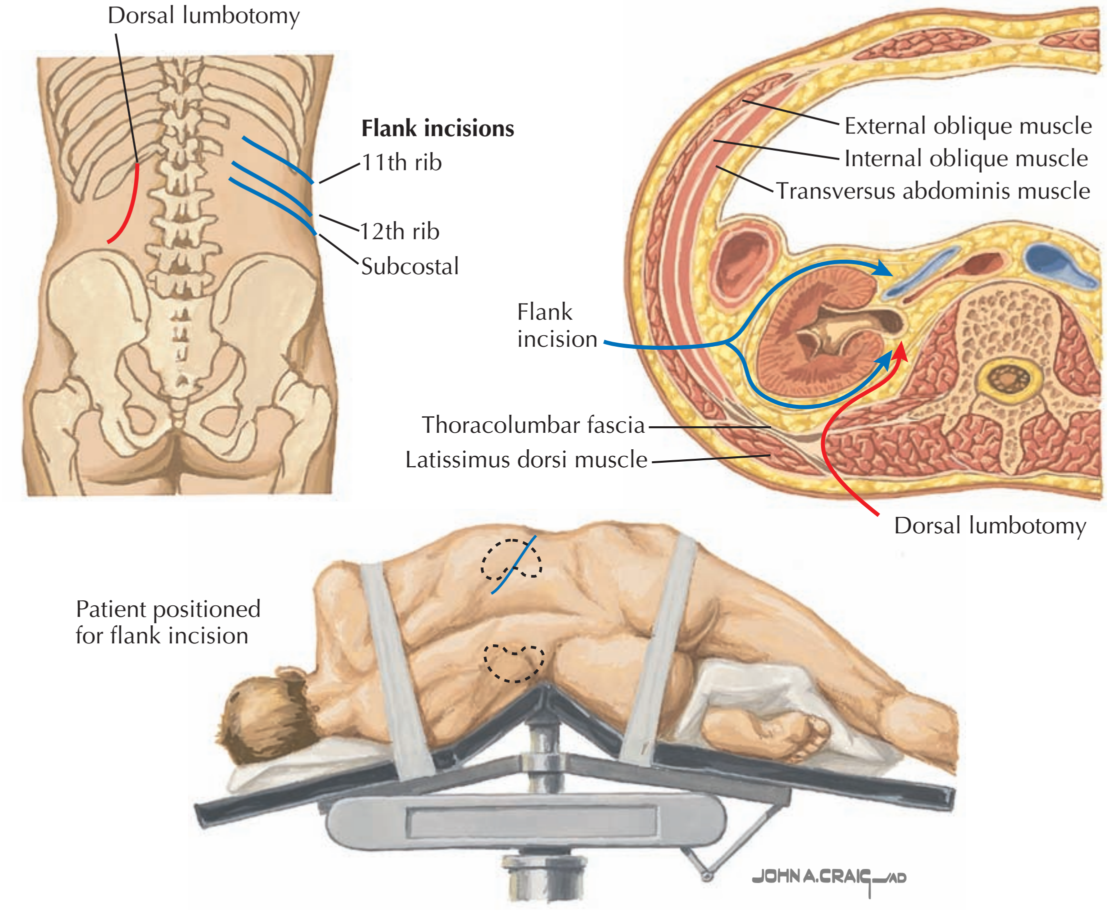
Patients who have recurrent stenosis after endovascular repair often require surgical revascularization. The surgical approach may be more challenging because of perivascular inflammation associated with the initial endovascular procedure; however, this difference does not appear to lower the probability of a successful outcome. Patients with recurrent stenosis after an initial surgical revascularization may undergo another surgical procedure with an alternative bypass route.

OPEN NEPHRECTOMY: INCISIONS FOR TRANSPERITONEAL AND RETROPERITONEAL APPROACHES

Transperitoneal approach


Thoracoabdominal incision
Midline
Chevron
Anterior subcostal
Midline, chevron, or anterior subcostal incision
Colon reflected from lateral peritoneal wall and anterior surface of renal fascia

Retroperitoneal approach


Dorsal lumbotomy
Flank incisions
11th rib
12th rib
Subcostal
External oblique muscle
Internal oblique muscle
Transversus abdominis muscle
Flank incision
Thoracolumbar fascia
Latissimus dorsi muscle
Dorsal lumbotomy
Patient positioned for flank incision
JOHN A.CRAIG AD

SIMPLE AND RADICAL NEPHRECTOMY

Simple nephrectomy refers to the surgical removal of the kidney without the renal fascia or ipsilateral adrenal gland. This technique may be employed to treat nonneoplastic, irreversible kidney disease that poses an ongoing threat to the patient's health. Possible indications include chronic pyelonephritis, chronic renal obstruction, extensive untreated nephrolithiasis, trauma, and ischemic nephropathy secondary to renal artery stenosis.

Radical nephrectomy, meanwhile, refers to the surgical removal of the kidney along with the perinephric fat, renal fascia, ipsilateral suprarenal gland, and ipsilateral retroperitoneal lymph nodes. Radical nephrectomy is the treatment of choice for patients with renal malignancies.

Both simple and radical nephrectomy may be performed using either an open or laparoscopic technique. In many cases, the surgeon will approach a simple nephrectomy with the same surgical strategy as a radical nephrectomy. Simple nephrectomies, however, may be technically more difficult because of the tissue fibrosis that commonly occurs secondary to chronic inflammation.

OPEN TECHNIQUE

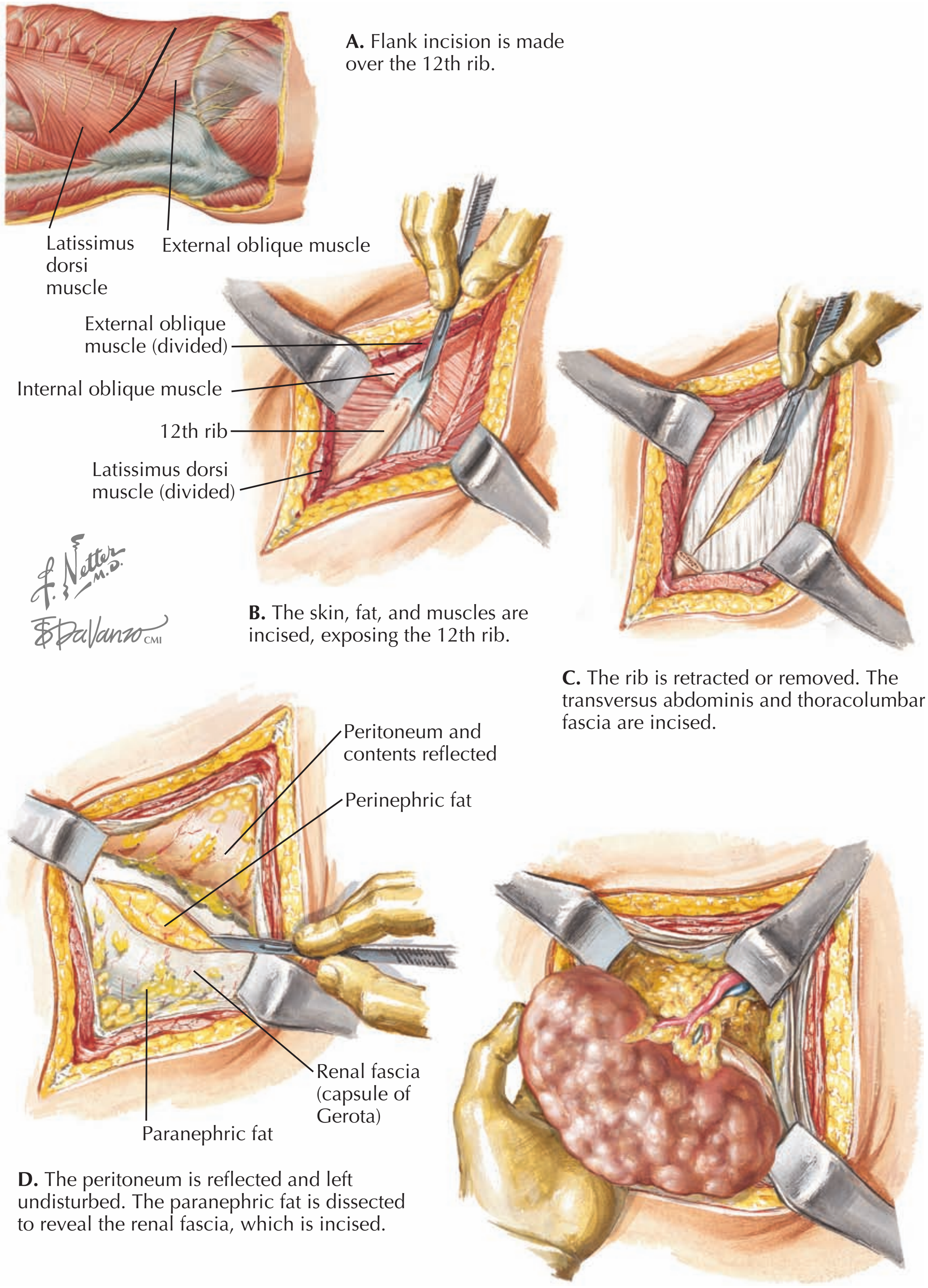
An open nephrectomy may be performed from a transperitoneal or retroperitoneal approach.

Transperitoneal Approach. The anterior subcostal and chevron incisions are the standard incisions for the transperitoneal approach. For both, the patient is placed in supine position, and an incision is made approximately two fingerbreadths below the costal margin. The incision extends from the anterior axillary line either to the xiphoid process (anterior subcostal incision) or to the opposite anterior axillary line (chevron incision). The dissection is carried down through the flank musculature (latissimus dorsi, external oblique, internal oblique, transversus abdominis), anterior rectus fascia, and rectus abdominis muscles. The round ligament of the liver (ligamentum teres) is clamped and ligated. The colon is mobilized medially, and then the plane between the colonic mesentery and renal fascia is developed. The renal hilum is approached anteriorly, and the vessels are ligated using a combination of silk suture and surgical clips. The ureter is identified and ligated. The upper pole of the kidney is separated from the adrenal gland if desired.

A midline transperitoneal incision may be used for patients undergoing exploratory laparotomy for trauma, during which an indication for nephrectomy may be discovered. It is not a common incision in planned surgeries on the kidney, however, because the surgeon is often forced to operate caudal to the kidney. Such an approach can make it difficult to achieve control of the hilar vessels, especially in obese patients.

A thoracoabdominal incision is used when radical nephrectomy is required in a patient with a large, right-sided upper pole tumor. The main advantage to this approach is the excellent exposure of the suprarenal area because inadequate retraction of the liver from

Open Simple Nephrectomy: Flank Approach



A. Flank incision is made over the 12th rib.

B. The skin, fat, and muscles are incised, exposing the 12th rib.

C. The rib is retracted or removed. The transversus abdominis and thoracolumbar fascia are incised.

D. The peritoneum is reflected and left undisturbed. The paranephric fat is dissected to reveal the renal fascia, which is incised.

E. The renal hilum is exposed and then divided.

SIMPLE AND RADICAL NEPHRECTOMY *(Continued)*

another approach could impede vascular control and complicate removal of a large mass. The incision begins in the eighth or ninth right intercostal space near the angle of the rib and is carried medially to the midpoint of the left rectus muscle. The dissection is carried down to the pleura and diaphragm, which are circumferentially incised to expose the liver. The liver is then fully mobilized and retracted cephalad. Next, the duodenum is mobilized medially to expose the kidney and hilum. After the kidney is removed, the diaphragm must be sutured, a chest tube placed, and the pleura repaired. This approach is associated with a considerable risk of injury to the lung, and there is also significant postoperative morbidity associated with the use of a chest tube. Therefore, this approach should be reserved only for large, right-sided upper pole tumors that cannot be safely removed with an anterior subcostal or chevron incision.

The major advantages to transperitoneal open access include the excellent exposure to the renal hilum and a large surgical field, whereas the disadvantages include the risk of adjacent organ injury and of prolonged ileus.

Retroperitoneal Approach. The flank incision is the standard incision for the retroperitoneal approach. The patient is placed in the lateral position after induction of anesthesia, with the table flexed at the level of the twelfth rib to maximize the space between the costal margin and the iliac crest. An incision is made directly over the eleventh or twelfth rib starting posteriorly at the lateral edge of the erector spinae muscles. The rib chosen for dissection and possible removal is the one nearest the hilum, which can be determined most accurately on cross-sectional imaging. (The original method for making this determination was to draw a horizontal line on an intravenous pyelogram from the hilum to the most lateral rib the line intersects.) Dissection is carried through the latissimus dorsi, external oblique, and internal oblique musculature to the rib, which may be either retracted or resected. The transversus abdominis muscle and tendon of origin, as well as the thoracolumbar and transversalis fascia, are then incised to expose the paranephric fat. The peritoneum is identified and swept medially with manual dissection to separate it from the paranephric fat, which is then dissected to expose the renal fascia. In the case of a simple nephrectomy, the renal fascia is entered along its lateral surface. The kidney is pulled laterally to reveal the renal vessels and ureter, which are ligated. The kidney is then removed.

A dorsal lumbotomy incision can be used when retroperitoneal access to the kidney is desired in patients who have fibrosis associated with prior abdominal or flank incisions. The incision is started over the erector spinae muscles at the level of the twelfth rib, then continued downward and laterally toward the iliac crest. The thoracolumbar fascia is incised lateral to the quadratus lumborum and erector spinae muscles, which are retracted medially. The transversalis fascia is then divided to expose the paranephric fat. An advantage of this approach is that it avoids transection of the abdominal muscles; however, it provides limited access to the hilum, making it difficult to control vascular complications.

The major advantages of retroperitoneal open access include the avoidance of the peritoneal space, which

SIMPLE AND RADICAL NEPHRECTOMY *(Continued)*

reduces the rate of injury to intraabdominal organs and the risk of postoperative ileus. The major disadvantage is that the renal vessels are not as easily visualized as in a transperitoneal approach.

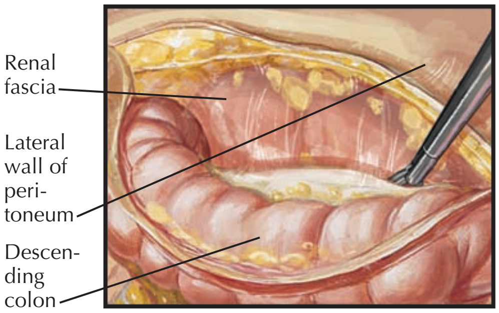
LAPAROSCOPIC TECHNIQUE

A laparoscopic nephrectomy can also be performed from either a transperitoneal or retroperitoneal approach.

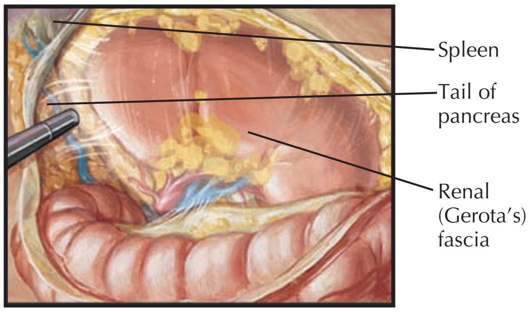
With a transperitoneal approach, the first step is to access the peritoneal cavity and establish a pneumoperitoneum using a Veress needle or open Hasson technique. After adequate insufflation of the abdomen, the first trocar is placed blindly into the abdomen. The laparoscope is inserted and the abdominal contents inspected for potential injury. Subsequent trocars are then inserted under direct laparoscopic vision. The number and configuration of trocars vary according to individual surgeon preference, but the basic principles of renal triangulation should be observed. The colon is mobilized medially and released of its attachments to the liver or spleen. The kidney is then retracted laterally to facilitate identification of the ipsilateral psoas muscle, gonadal vein, and ureter. The renal artery and vein are carefully dissected to determine if there are accessory vessels or segmental vessel branches, then the artery and any accessory branches are ligated using a laparoscopic surgical stapling device. Additional dissection is performed to confidently eliminate all bleeding from the arterial stump. The vein is targeted and ligated in the same manner, then the ureter is divided. The upper pole of the kidney is separated from the adrenal gland as needed. Finally, the kidney is placed in a laparoscopic collection bag and removed through either an extension of a trocar incision or through a separate skin incision (typically Pfannenstiel). The pneumoperitoneum is reduced to ensure adequate hemostasis, and the trocar sites are closed.

With a retroperitoneal approach, the first step is to make a small incision over the tip of the twelfth rib. A surgical clamp is then used to puncture the thoracolumbar fascia and enter the retroperitoneum. Manual dissection is performed to free additional space, and the psoas muscle is located using tactile feedback. Next, a balloon trocar is placed in the space and inflated to expand the surgical field. The space is then insufflated, and additional trocars are inserted. The kidney is mobilized by separating the psoas muscle from the paranephric fat and renal fascia. The renal hilum is then identified and divided, as noted earlier.

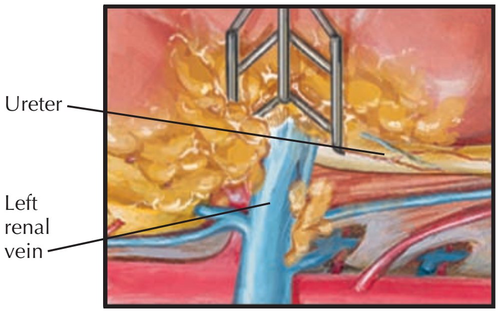
LAPAROSCOPIC RADICAL NEPHRECTOMY: TRANSPERITONEAL APPROACH (LEFT-SIDED)



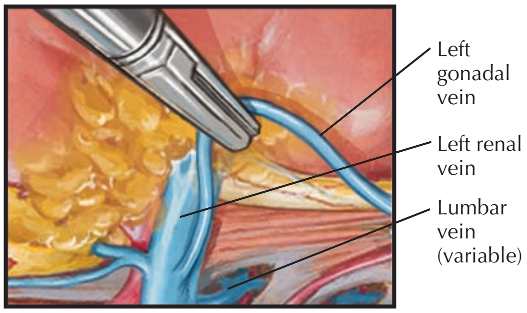
1. The colon is reflected from the peritoneal wall and the anterior surface of the renal fascia.



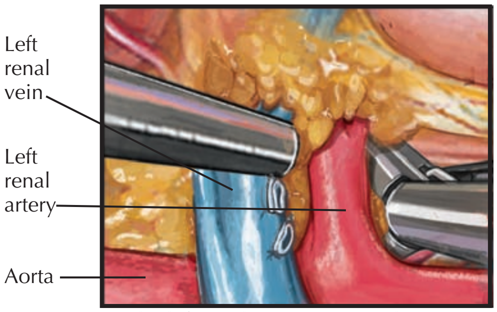
2. The cranial end of the renal fascia is freed from the stomach, spleen, and tail of the pancreas.



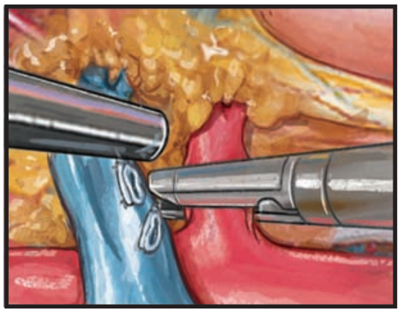
3. The kidney is put on lateral tension to facilitate identification of the gonadal vein and ureter.



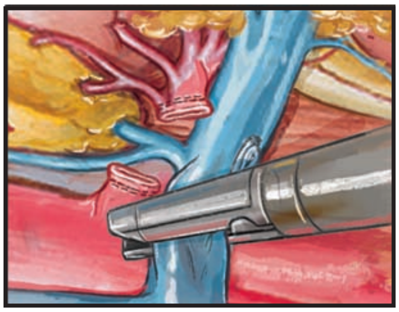
4. The left gonadal vein is identified, followed to its origin from the left renal vein and may be divided.



5. The left renal vein is retracted to expose the left renal artery, which is dissected free.

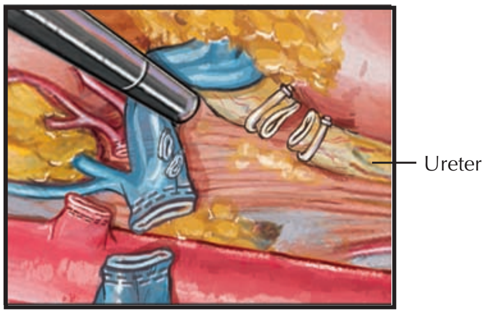


6. The left renal artery is divided using a laparoscopic stapler.



7. The left renal vein is then divided proximal to the adrenal vein.

F. Netter M.D.
DaVanzo CMI



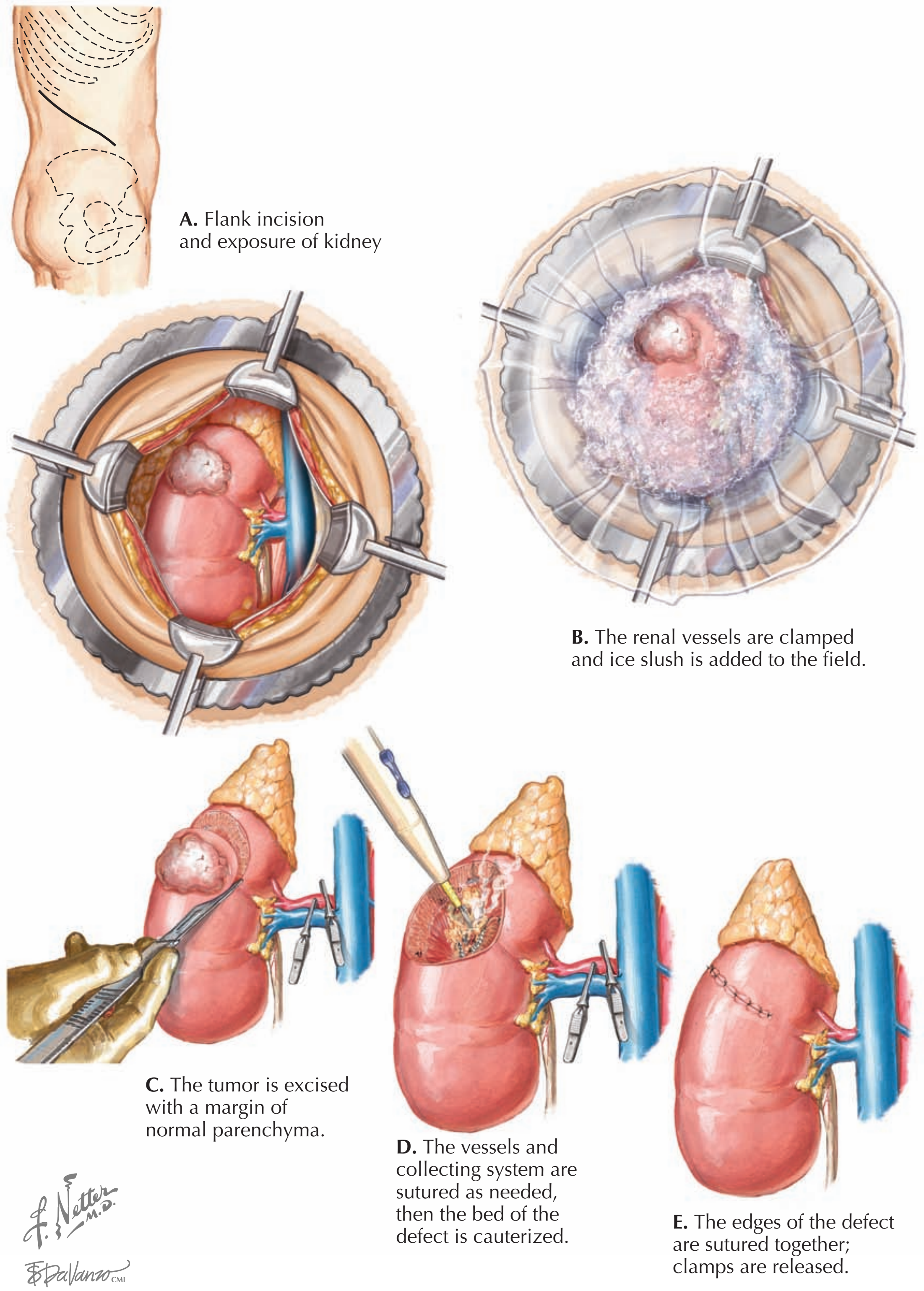
8. The ureter is clipped and divided. Dissection is carried around the renal fascia until all remaining attachments are ligated, freeing the kidney, adrenal gland, and surrounding fascia for removal in an entrapment bag.

COMPLICATIONS

The complications associated with nephrectomy include standard surgical complications, such as bleeding, infection, wound separation, myocardial infarction, cerebral vascular accident, deep vein thrombosis, pulmonary embolus, cardiac dysrhythmia, ileus, and atelectasis. In addition, several complications are specific to this procedure, including renal insufficiency and injury to adjacent organs (perforation of bowel, disruption of retroperitoneal vasculature, pancreatic ductal injury/fistula formation, pneumothorax).

Laparoscopic approaches in particular can be complicated by visceral or vascular injuries during initial access with the Veress needle or trocars. In addition, patients should always be warned that all laparoscopic cases have the potential for conversion to an open procedure.

Open Partial Nephrectomy: Retroperitoneal (Flank) Approach



A. Flank incision and exposure of kidney

B. The renal vessels are clamped and ice slush is added to the field.

C. The tumor is excised with a margin of normal parenchyma.

D. The vessels and collecting system are sutured as needed, then the bed of the defect is cauterized.

E. The edges of the defect are sutured together; clamps are released.

PARTIAL NEPHRECTOMY

Although radical nephrectomy is the standard surgical treatment for large renal tumors, nephron-sparing surgery has become the new standard of care for small (<4.0 cm) renal masses (SRMs).

In a partial nephrectomy, the renal tumor and a small margin of normal tissue are removed. The remainder of the parenchyma is spared, so as to preserve renal function. Although partial nephrectomy offers benefits to all patients with SRMs, it is especially beneficial for patients with multiple or bilateral masses, tumors in a solitary kidney, or medical diseases that threaten future kidney function.

There is substantial evidence that for tumors ≤4.0 cm in diameter, partial nephrectomy provides oncologic outcomes that are comparable to those of radical nephrectomy. The potential for tumor recurrence or progression to metastatic disease is low, with 10-year cancer-specific survival rates between 87% and 90% in large patient series.

EVALUATION

The preoperative evaluation should include basic laboratory tests (complete blood count, serum chemistries, liver function tests), a chest radiograph, and comprehensive axial imaging of the abdomen (either CT or MRI) with renal protocols. Patients should receive counseling on all available management options, which include active surveillance, partial nephrectomy, percutaneous ablation (see Plate 10-24), and radical nephrectomy (see Plate 10-20). In elderly patients or patients with significant medical comorbidities, ablation or active surveillance are often more appropriate choices because of the high risk of perioperative complications. Patients must be informed of the potential for a planned partial nephrectomy to become a radical nephrectomy based on the operative course.

TECHNIQUE

Partial nephrectomy may be performed from either an open or laparoscopic approach. Both techniques are equally effective for the treatment of a renal mass, but laparoscopic partial nephrectomy is typically associated with less blood loss, less pain, a lower risk of postoperative ileus, and a shorter hospitalization and overall convalescence time. In addition, laparoscopic procedures require smaller skin incisions, which yield better cosmetic results.

Both open and laparoscopic partial nephrectomy procedures may be performed using transperitoneal or retroperitoneal (flank) approaches. The different incision sites, as well as the techniques for approaching the kidney, are the same as described in the section on simple and radical nephrectomy (see Plate 10-21).

Once visualized, the renal fascia should be mobilized free of its attachments and then opened and dissected. The renal hilum should be carefully identified and exposed. The tumor should be accurately localized using a combination of high-quality preoperative imaging, intraoperative visualization, and intraoperative ultrasonography (which establishes the location and depth of the lesion in three dimensions). Using intraoperative color Doppler ultrasound, it should be confirmed that occlusion of the renal vessels results in complete interruption of blood flow to the tumor and surrounding parenchyma.

Once the tumor has been characterized, intravenous mannitol should be infused to help minimize renal ischemic injury during tumor excision. Mannitol increases renal plasma flow, reduces intracellular edema, and promotes osmotic diuresis to flush out debris and casts from the renal tubules (see Plate 10-1).

PARTIAL NEPHRECTOMY

(Continued)

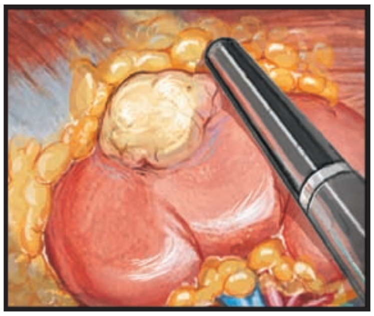
Open Partial Nephrectomy (OPN). Approximately 5 to 15 minutes after the administration of mannitol, the renal artery and vein are clamped using atraumatic bulldog vascular clamps. An ice-slush mixture is placed around the kidney for approximately 10 minutes so that it is cooled to 20° to 25° C. This process reduces metabolic demands and slows the consumption of oxygen, permitting up to 3 hours of renal artery clamping without long-term ischemic damage.

Once cooling is complete, the tumor is excised using a scalpel or Metzenbaum scissors, allowing for a margin of normal parenchyma around the excised mass. The removal of endophytic tumors often leads to collecting system injury, which requires reconstruction using absorbable sutures. Bleeding is surgically controlled with absorbable sutures. The bed of the cortical defect is cauterized using standard electrocautery or an argon beam coagulator. Hemostatic agents are placed on the parenchyma, and the renal capsule is closed using interrupted absorbable sutures. The vascular clamps are then removed, hemostasis is confirmed, and the surgical field is closed.

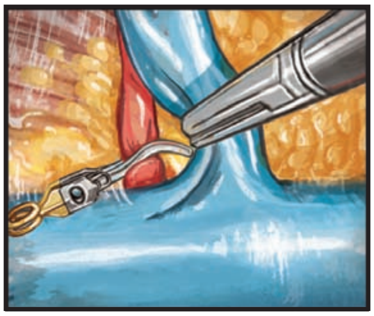
Laparoscopic Partial Nephrectomy (LPN). Five to fifteen minutes after the administration of mannitol, the renal artery is clamped using an atraumatic bulldog vascular clamp. Renal parenchymal hypothermia remains a challenge during laparoscopic partial nephrectomy because of the logistical challenges of introducing ice into the field. Therefore, the renal vein is typically left patent, which may help minimize ischemic damage by allowing retrograde perfusion of the kidney. Excessive bleeding is usually not a concern because of the tamponade effect of the pneumoperitoneum.

The tumor is excised using laparoscopic scissors. Collecting system defects are repaired, and the bed of the defect is cauterized. Any further bleeding is controlled using absorbable sutures and hemostatic agents. The parenchymal defect is then closed. The vascular clamps are removed, and hemostasis is again confirmed. The pneumoperitoneum is reduced to ensure that bleeding does not occur without its tamponade effect. The tumor is then removed intact in an entrapment bag, and the trocar sites are closed.

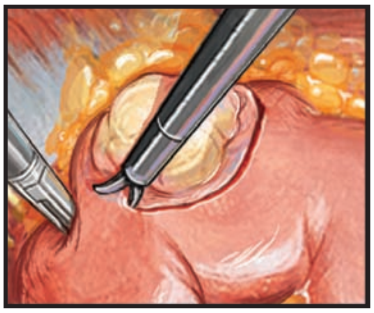
LAPAROSCOPIC PARTIAL NEPHRECTOMY: TRANSPERITONEAL APPROACH



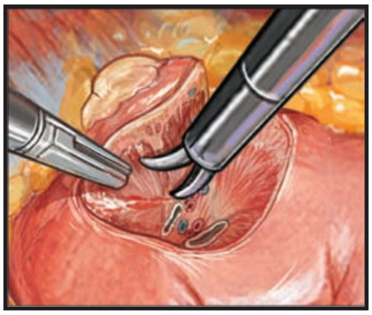
1. The tumor is identified and characterized using laparoscopic ultrasound.



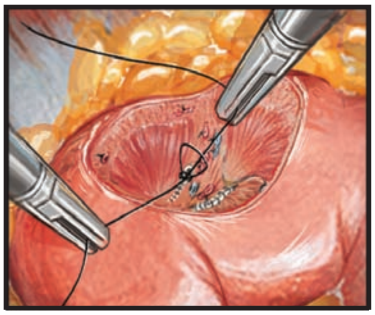
2. The renal artery is clamped.



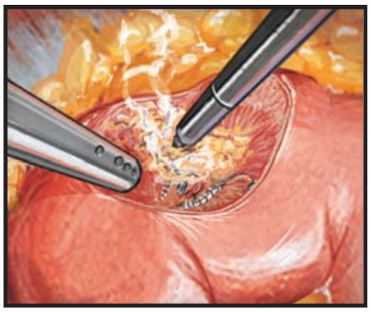
3. Using laparoscopic scissors, incision of the tumor (with a rim of normal parenchyma) begins.



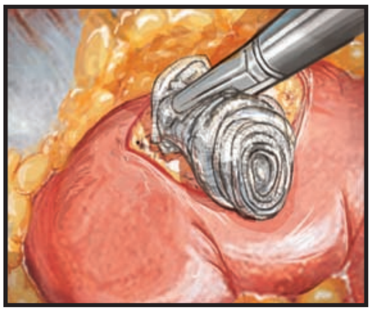
4. Dissection continues until the tumor is completely detached from the kidney.



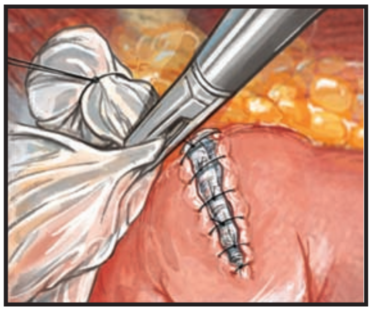
5. The collecting system is repaired using reabsorbable sutures.



6. Electrocautery or argon beam device is used to coagulate the cortical aspects of the defect.



7. Hemostatic agents are placed in the defect.



8. The defect in the renal parenchyma is closed, and the tumor is removed intact in an entrapment bag.

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DaVanzo CMI

COMPLICATIONS

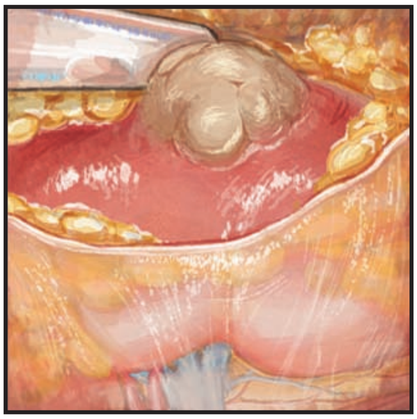
At present there is no difference in complication rates between open and laparoscopic partial nephrectomy. The most common postoperative complications are bleeding and urine leak (urinoma).

In situations where postoperative bleeding is suspected, the patient should be managed with serial complete blood counts, bed rest, and blood transfusions as needed. Conservative measures are often adequate when the bleeding is modest, but interventions such as selective arterial embolization or surgical reexploration may sometimes be required.

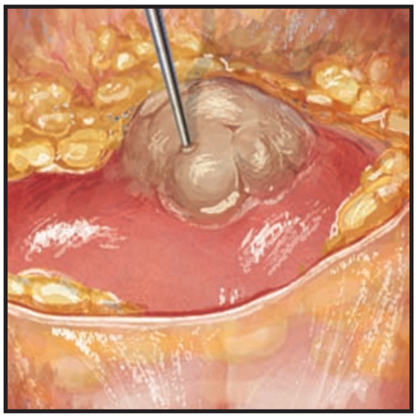
Urine leakage can result from inadequate intraoperative closure of a collecting system defect or ureteral obstruction from a blood clot, which increases backflow pressure. A surgical drain should therefore be used when the renal collecting system has been violated to monitor for postoperative leak. In addition, the patient should retain a Foley catheter to ensure bladder decompression and low upper tract pressure. Urine leaks are usually transient and heal without intervention; however, a persistent leak may require the placement of a ureteral stent to facilitate drainage and healing.

In addition to bleeding and urine leak, other potential complications include wound infection, ileus, pneumonia, injury to adjacent organs, and transient renal insufficiency.

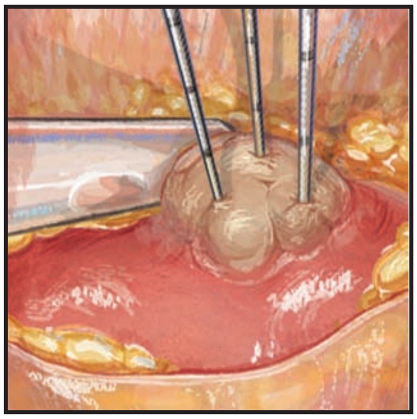
LAPAROSCOPIC CRYOABLATION: RETROPERITONEAL APPROACH



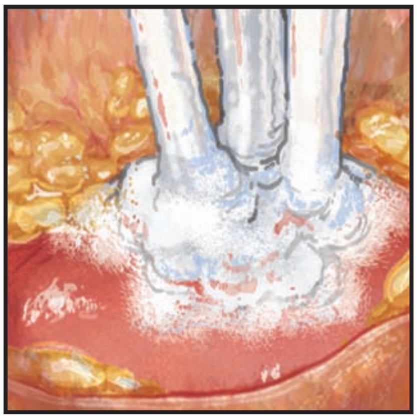
1. The renal fascia is opened and the perinephric fat carefully removed to expose the tumor, which is further characterized using laparoscopic ultrasound.



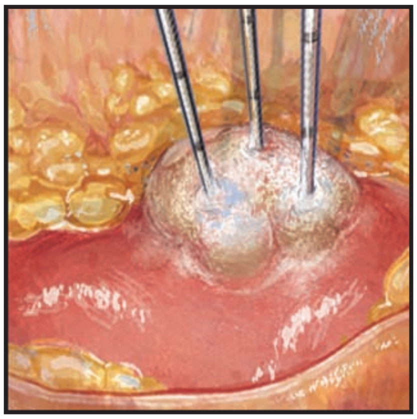
2. Multiple percutaneous needle biopsies are performed.



3. The cryoprobes are placed into the tumor under direct vision, and laparoscopic ultrasound is used to confirm that their tips extend past the internal border of the tumor.



4. The first freeze-thaw cycle begins. Freezing continues until the ice ball extends at least one centimeter beyond the gross tumor margins.



5. The ice ball is allowed to thaw prior to initiation of the second freeze-thaw cycle.

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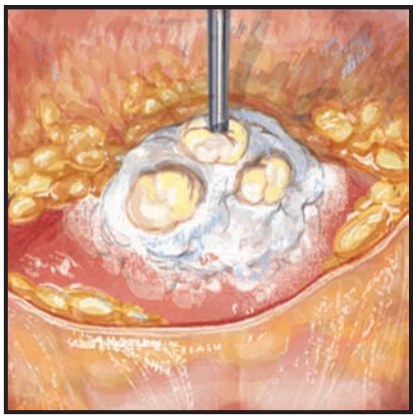


6. After the second freeze-thaw cycle, the cryoprobes are removed, and surgical hemostatic pharmaceutical is applied to the insertion sites.

RENAL ABLATION

Nephron-sparing surgery has become the standard of care for patients with small (<4.0 cm) renal masses (SRM). For young, healthy patients with a low surgical risk, open or laparoscopic partial nephrectomy (OPN/LPN) is preferred. Renal tumor ablative techniques, however, are relatively new developments with increasing application. Such techniques were initially indicated in patients with multiple renal tumors, a solitary kidney, or significant comorbidities that precluded higher risk surgery. In contemporary practice, however, sufficient evidence indicates that ablation may be a reasonable treatment option for all patients with SRMs. The advantages of renal ablation over LPN include less blood loss, shorter hospitalization time, decreased postoperative pain, and a lower complication rate.

ABLATION MODALITIES

At present, the clinically viable ablation technologies include cryoablation and radiofrequency ablation. Either can be performed using laparoscopic or percutaneous technique. Both involve placement of probe needles directly into the renal mass.

In cryoablation, the cryoprobe needles are cooled to very low temperatures, which induces tissue necrosis. At present, such cooling is achieved by delivering pressurized argon gas to the tips of the cryoprobes. As argon gas passes through the restricted tips of the probes and then expands, it undergoes rapid cooling (a phenomenon known as the Joule-Thomson effect) and forms an iceball over the tumor. The temperature at the probe tip becomes as low as −140° to −190° C, whereas the temperature at the edge of the ice ball is just below 0° C. Since the temperature required for cell destruction is between −20° and −40° C, the efficacy of the ablation process declines in a gradient radiating from the tips of the probes toward the edges of the iceball. Therefore, the iceball must involve a margin of normal tissue to ensure complete tumor destruction. Following the freeze cycle, an active thaw phase is initiated, and then a second freeze-thaw cycle is performed to further increase cell death.

In radiofrequency ablation (RFA), the probes transfer high-frequency electrical current to the target tissue, which results in the production of thermal energy. Temperatures in excess of 60° C cause tissue destruction through coagulative necrosis and thermally induced vascular thrombosis.

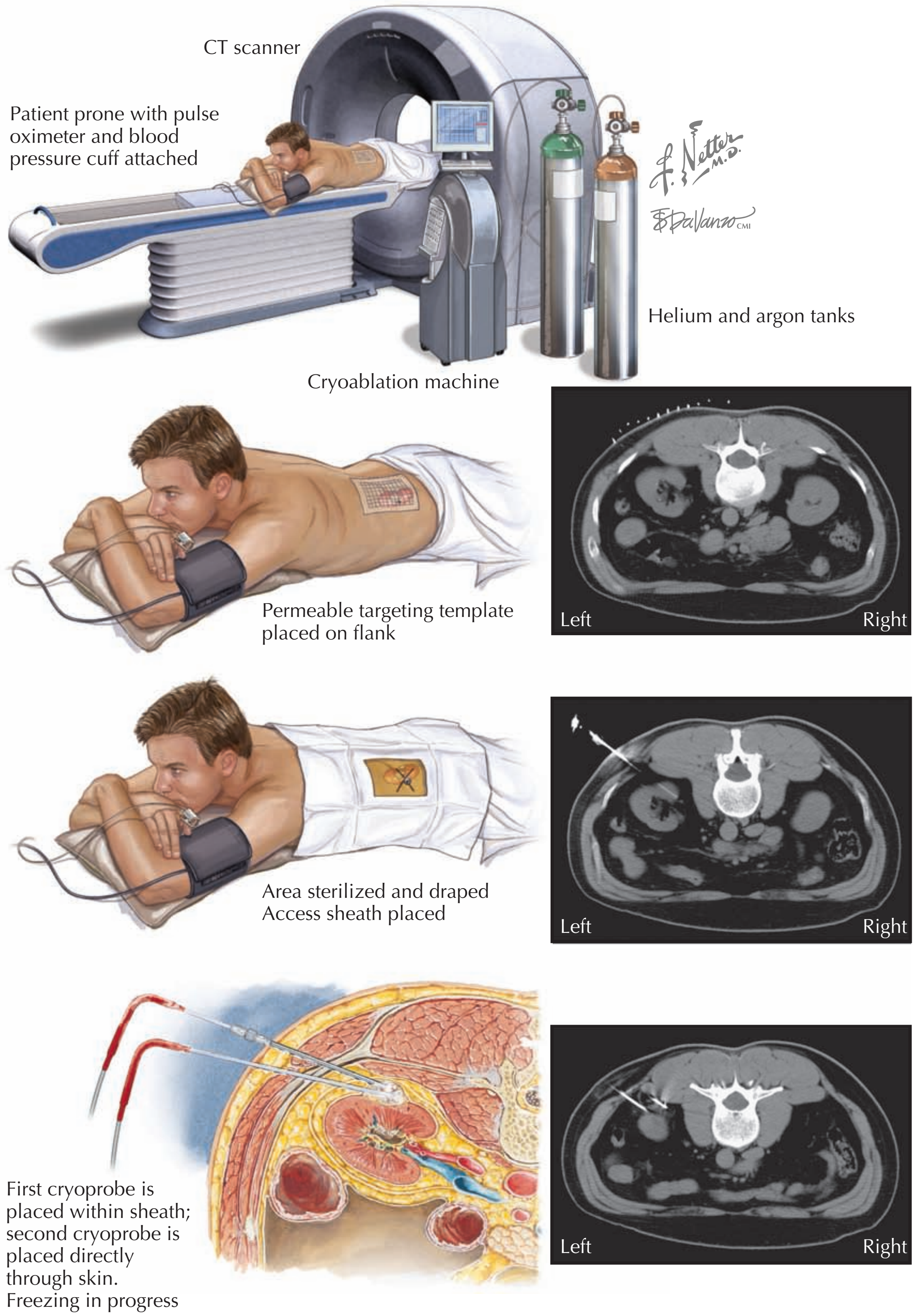
High-intensity focused ultrasound (HIFU) is an experimental extracorporeal procedure in which focused ultrasound waves pass through the skin and are converted to heat energy at a selected target. Contemporary HIFU technologies, however, have not demonstrated adequate oncologic efficacy and are thus not yet part of standard clinical practice.

TECHNIQUE

Laparoscopic Technique. In a laparoscopic ablation, the tumor can be directly visualized, and the ablation process can be monitored in real time.

The tumor can be accessed from either a transperitoneal or retroperitoneal approach, depending on its location. In the transperitoneal approach, the colon is mobilized medially to expose the renal fascia, which is mobilized from its attachments to surrounding structures, such as the liver or spleen. Next, the renal fascia is entered over the area of the renal mass, which is targeted using preoperative imaging and intraoperative ultrasound. The perirenal fat is then carefully removed from

PERCUTANEOUS CRYOABLATION


CT scanner
Patient prone with pulse oximeter and blood pressure cuff attached
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Helium and argon tanks
Cryoablation machine
Permeable targeting template placed on flank
Left
Right
Area sterilized and draped
Access sheath placed
Left
Right
First cryoprobe is placed within sheath; second cryoprobe is placed directly through skin. Freezing in progress
Left
Right

RENAL ABLATION *(Continued)*

the renal capsule to expose the entire surface of the tumor.

Once the tumor has been adequately visualized, multiple core biopsies are acquired using a percutaneous biopsy device. Intraoperative ultrasound is then performed to further characterize the tumor's depth and vascularity.

Finally, ablation probes are inserted through the skin and into the tumor under direct vision. The number of ablation probes that should be deployed depends both on the tumor's characteristics and the technology being applied. The probes should enter the tumor at a right angle, and laparoscopic ultrasound should be performed to ensure the probe tips are beyond the internal margin of the tumor. Once proper positioning has been achieved, the probes are activated.

During cryoablation, laparoscopic ultrasound can be used to monitor the iceball as it forms, ensuring that it completely engulfs the mass and a 1-cm rim of normal parenchyma. Two freeze-thaw cycles are performed, and then the probes are removed. To minimize the chance of bleeding, probe extraction should not be attempted until the probes are loose enough to freely twist within the tumor.

During RFA, the ablation process cannot be visualized in real time. Instead, the RF ablation process proceeds using temperature- or impedance-based algorithms that are device-specific. Alternatively, some clinicians deploy temperature probes at selected sites around the tumor to monitor the ablation process.

After the ablation process is completed, the lesion is monitored for hemorrhage, and minor bleeding is controlled using topical hemostatic agents and gentle pressure. After hemostasis has been confirmed at reduced pneumoperitoneum, the trocars are removed.

Percutaneous Technique. Percutaneous ablation offers numerous advantages over a laparoscopic procedure, including avoidance of general anesthesia, reduced complication rate, diminished postoperative pain, and expedited convalescence. The major disadvantages, however, include the lack of direct visualization during the ablation process, as well as the inability to assess for immediate postablation bleeding.

Percutaneous ablation may be performed in a CT or magnetic resonance imaging (MRI) suite. The patient is placed under conscious sedation and positioned prone. A semipermeable targeting template is positioned over the ipsilateral flank, and imaging is performed to correlate the template with the renal anatomy. The targeting template is marked to indicate the location where the needles should be inserted, and then the template is removed so that the mark is visible on the patient's skin. The site is sterilized and draped in standard fashion. An access sheath is then deployed at the marked site, and its position in the kidney is confirmed and readjusted if necessary using imaging. Several tumor biopsies are acquired through the access sheath. The first probe is then placed through the access sheath. Subsequent probes are placed directly through the skin, with additional imaging performed to confirm proper positioning. The ablation is then performed. Once completed, a final image series is acquired using a half dose of intravenous contrast to confirm successful tumor ablation.

COMPLICATIONS

Both cryoablation and RFA tend to have lower complication rates than OPN/LPN. Nonetheless, they carry a risk of some major complications, including bleeding from the tumor, injured intraabdominal vessels, or skin; pain at the trocar or probe sites; urinary tract infection; intraabdominal abscess; ileus; injury to adjacent organs; and tumor persistence or recurrence after treatment.

RENAL TRANSPLANTATION

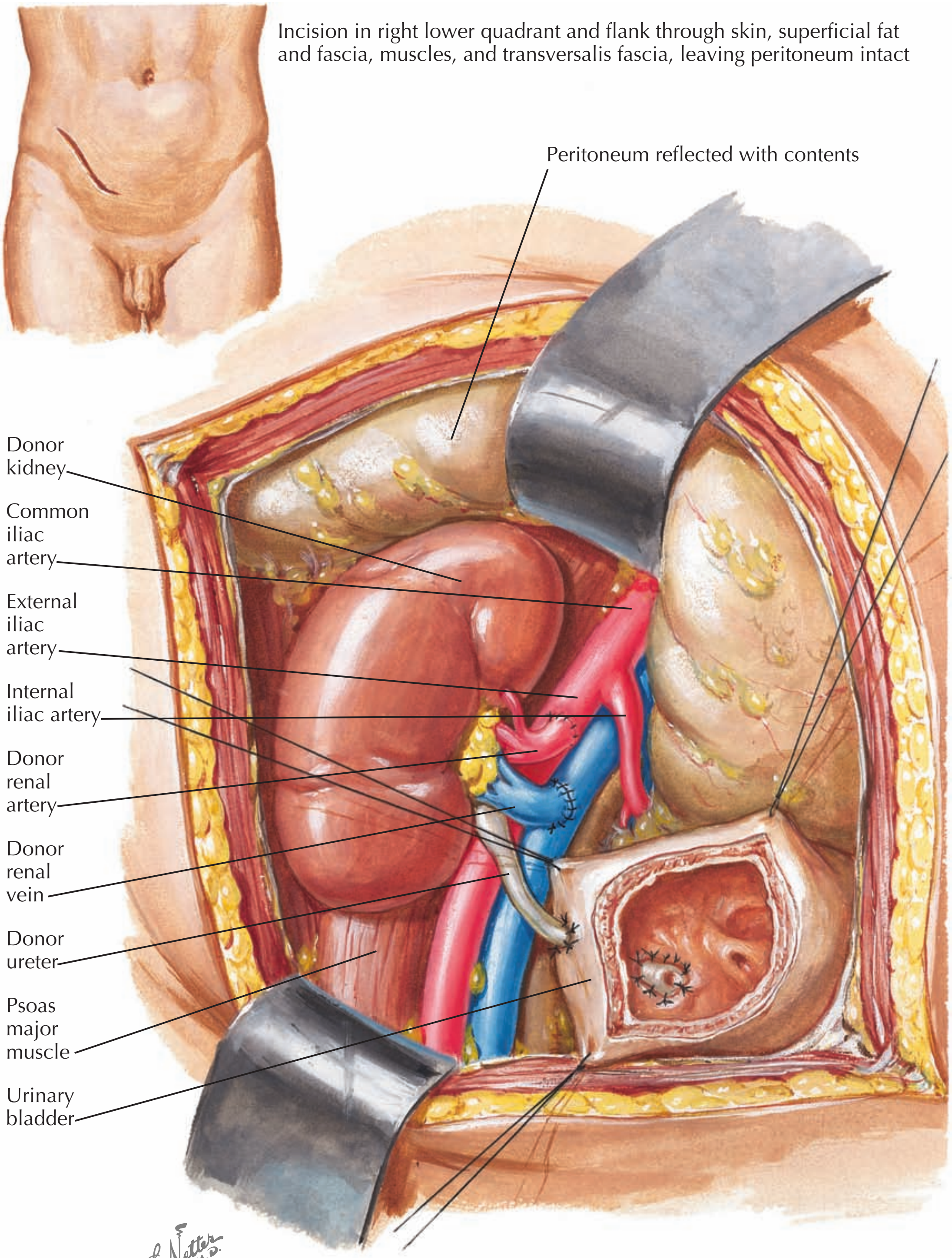
The concept of replacing a diseased human organ with tissue from a living or deceased person has existed since ancient times. The different kinds of transplanted tissue include an autograft (tissue from the recipient), an isograft (tissue from an individual with the same genotype, such as a monozygotic twin), an allograft (tissue from a genetically disparate individual from the same species), and a xenograft (tissue from a different species).

As early as 1916, Little and Tyzzer articulated the important differences between these graft types, stating “isografts succeed; allografts are rejected.” A century later, the clinical practice of transplantation remains subject to these laws. Nonetheless, the introduction of modern immunosuppression drugs has led to dramatic improvements in allograft outcomes. As a result, kidney transplantation has become a common intervention.

Unfortunately, only a small minority of the patients that would benefit from a kidney transplant ever receive one. There is an ever-growing waiting list—84,355 patients in the United States in 2010—that far exceeds the number of annual procedures. In 2009, 16,830 kidney transplants were performed: 10,442 from a deceased donor, and 6388 from a living donor.

Despite the growing need for organs, the number of deceased organ donors per year has been stagnant. Nonetheless, the annual number of kidney transplants continues to rise. Much of this growth has been fueled by an increase in live donors, in large part because of substantial improvements in the organ harvesting process, such as the introduction of minimally invasive techniques.

RECIPIENT OPERATION IN KIDNEY TRANSPLANTATION



Incision in right lower quadrant and flank through skin, superficial fat and fascia, muscles, and transversalis fascia, leaving peritoneum intact

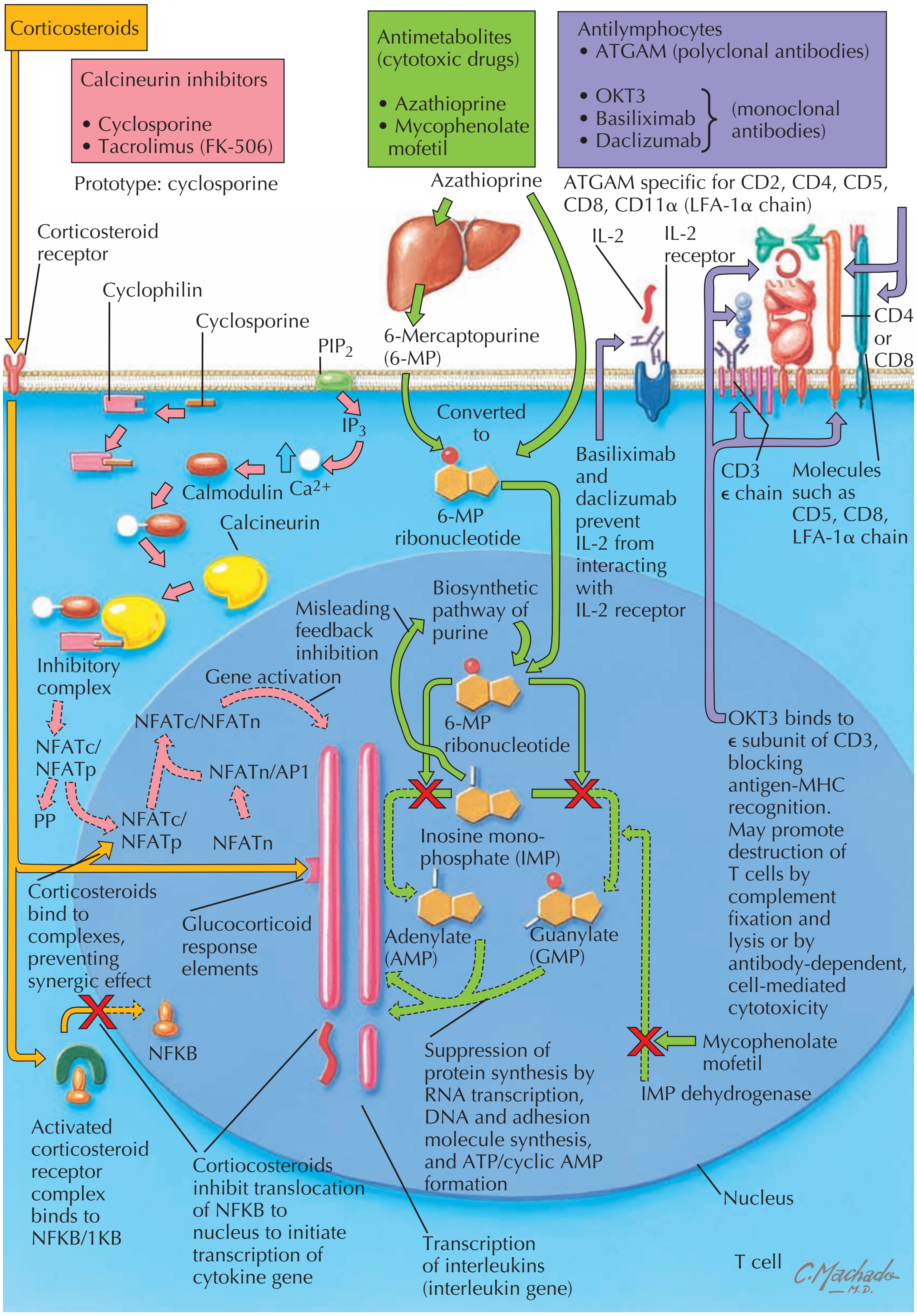
Donor kidney implanted in iliac fossa; renal artery anastomosed end to side with external iliac artery; renal vein end to side with external iliac vein; ureter implanted into bladder

INDICATIONS, DONOR MATCHING, AND PREOPERATIVE EVALUATION

All patients with either end-stage renal disease or advanced chronic kidney disease (stage 4 or 5) should be considered for renal transplantation. Those who can tolerate the surgical and anesthetic risks, and who can safely be immunosuppressed after the transplant, are potential candidates. Relative contraindications include uncorrectable advanced cardiopulmonary disease, cirrhosis, active malignancies, active infections, active substance abuse, and inadequate social support.

Before transplantation, the donor and recipient must be confirmed to have compatible blood types. In addition, precautions must be taken to ensure immune compatibility. Recipient serum must be tested against donor lymphocytes to ensure the recipient does not have preformed antibodies to donor proteins. The problematic alloantibodies are most commonly directed against donor major histocompatibility complex (MHC) class I and class II antigens. MHC class I antigens are expressed on most nucleated cells, albeit at variable levels, whereas MHC class II antigens are expressed mainly on antigen presenting cells (B lymphocytes, dendritic cells, and some endothelial cells). Thus recipient serum is tested against donor lymphocytes, which contain both MHC antigens. A positive crossmatch predicts a high likelihood of hyperacute or early rejection.

Mechanism of Action of Immunosuppressive Medications in Kidney Transplantation


Corticosteroids
Calcineurin inhibitors
• Cyclosporine
• Tacrolimus (FK-506)
Prototype: cyclosporine
Antimetabolites (cytotoxic drugs)
• Azathioprine
• Mycophenolate mofetil
Antilymphocytes
• ATGAM (polyclonal antibodies)
• OKT3
• Basiliximab
• Daclizumab
(monoclonal antibodies)
ATGAM specific for CD2, CD4, CD5, CD8, CD11α (LFA-1α chain)
Corticosteroid receptor
Cyclophilin
Cyclosporine
PIP2
IP3
Azathioprine
6-Mercaptopurine (6-MP)
Converted to
IL-2
IL-2 receptor
CD4 or CD8
Calmodulin
Ca2+
Calcineurin
6-MP ribonucleotide
Basiliximab and daclizumab prevent IL-2 from interacting with IL-2 receptor
CD3 ϵ chain
Molecules such as CD5, CD8, LFA-1α chain
Inhibitory complex
Misleading feedback inhibition
Biosynthetic pathway of purine
Gene activation
NFATc/NFATn
NFATc/NFATp
NFATn/AP1
PP
NFATc/NFATp
NFATn
6-MP ribonucleotide
OKT3 binds to ϵ subunit of CD3, blocking antigen-MHC recognition. May promote destruction of T cells by complement fixation and lysis or by antibody-dependent, cell-mediated cytotoxicity
Inosine monophosphate (IMP)
Corticosteroids bind to complexes, preventing synergic effect
Glucocorticoid response elements
Adenylate (AMP)
Guanylate (GMP)
NFKB
Mycophenolate mofetil
IMP dehydrogenase
Suppression of protein synthesis by RNA transcription, DNA and adhesion molecule synthesis, and ATP/cyclic AMP formation
Activated corticosteroid receptor complex binds to NFKB/1KB
Cortiocosteroids inhibit translocation of NFKB to nucleus to initiate transcription of cytokine gene
Nucleus
Transcription of interleukins (interleukin gene)
T cell
C.Machado M.D.

RENAL TRANSPLANTATION

(Continued)

In the past, the human leukocyte antigen genes (HLA) of both donor and recipient, which encode the MHC genes, were also examined to determine the risk of later alloantibody production and delayed graft rejection. Because of the efficacy of current immunosuppressive therapies, however, there is a reduced need to ensure HLA matching between the donor and recipient. Moreover, acute rejection episodes that do occur can usually be effectively treated. Nonetheless, transplants between HLA-identical siblings continue to yield the best long-term outcomes.

Kidney transplants from living donors result in superior outcomes compared with those where the kidney has been obtained from a deceased donor. Proinflammatory and proapoptotic physiologic perturbations associated with death, as well as the increased cold ischemic times associated with deceased donor transplantation, account for this difference in outcome.

PROCEDURE

Whether procured from a living or deceased donor, kidneys for transplantation are flushed with cold (4° C) preservation solution until asanguinous. The use of cold organ preservation allows for successful transplantation even with extended ischemic times, which may exceed 48 hours. As a result, kidneys may be shipped over long distances to reach the recipient. Nonetheless, it is preferable to minimize ischemic times. Deceased donor kidneys may also be placed on a specialized mechanical perfusion apparatus that has been shown to decrease the incidence of delayed allograft function.

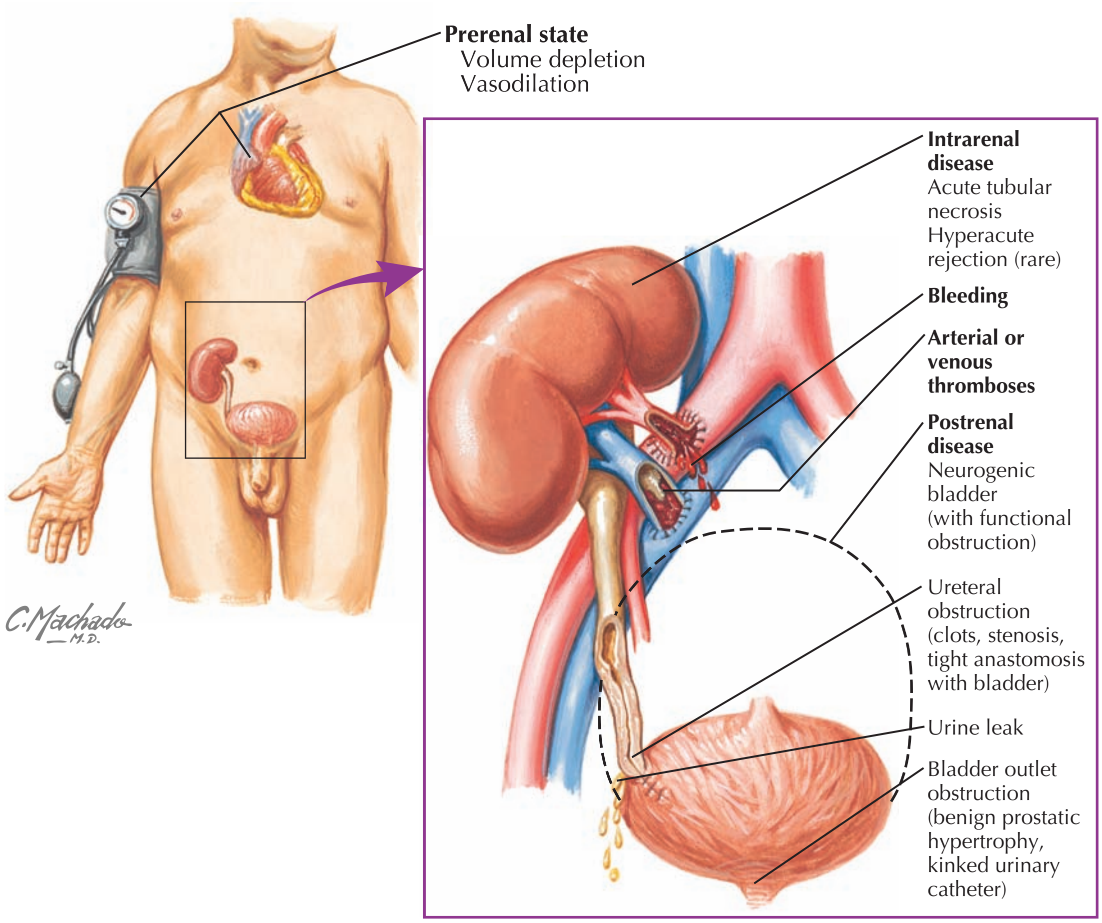
Before the harvested organ can be transplanted, surgeons must perform a functional assessment of the allograft and review the anatomic report of the procuring surgeon to determine if there are any tumors, vascular or ureteral anomalies, or traumatic injuries to the kidney that could preclude successful transplantation.

The recipient operation is usually a heterotopic transplant, meaning the recipient's kidneys are left in place and the transplanted kidney is placed in the iliac fossa, away from its normal anatomic position. The procedure is performed through a Gibson or "hockey stick" incision in one of the lower quadrants of the abdomen. A renal allograft can be implanted on either side, although many surgeons recommend implanting a left kidney in the right iliac fossa and vice versa. The advantage of this approach is that it positions the renal pelvis and ureter at the most anterior aspect of the renal hilum, which facilitates access if reconstruction is required at a later date.

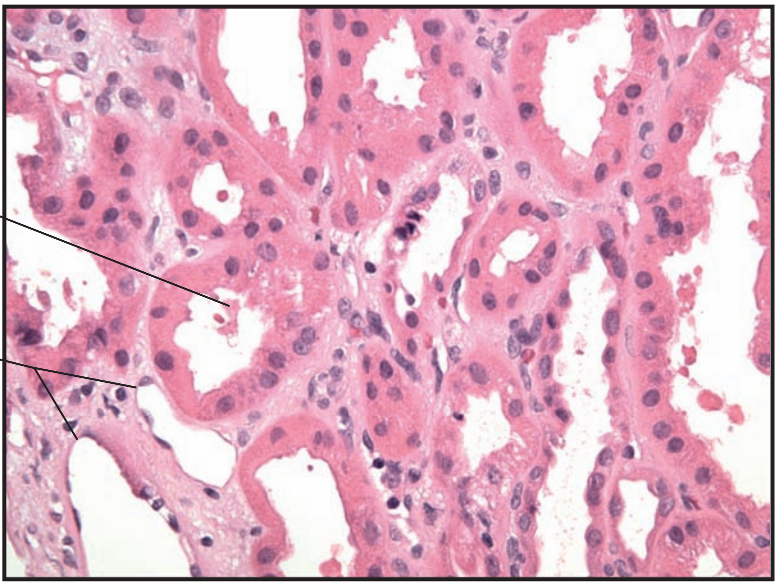
The fascia and muscle layers of the obliques and transversus are divided just lateral to the edge of the rectus abdominis sheath. The superficial epigastric artery can be either ligated and divided, or spared and mobilized medially. In females, the round ligament is divided to mobilize the peritoneum, which is moved superiorly and medially to uncover the external iliac artery and vein. In males, the spermatic cord structures are preserved and mobilized medially to allow retraction of the peritoneum from the abdominal wall.

Anastomosis is performed between the renal allograft vein and external iliac vein, then between the renal allograft artery and external iliac artery. The ends of the

CAUSES OF GRAFT DYSFUNCTION IN IMMEDIATE POST-TRANSPLANT PERIOD


Prerenal state
Volume depletion
Vasodilation
Intrarenal disease
Acute tubular necrosis
Hyperacute rejection (rare)
Bleeding
Arterial or venous thromboses
Postrenal disease
Neurogenic bladder (with functional obstruction)
Ureteral obstruction (clots, stenosis, tight anastomosis with bladder)
Urine leak
Bladder outlet obstruction (benign prostatic hypertrophy, kinked urinary catheter)
C.Machado M.D.

Acute tubular necrosis: histopathologic findings


Sloughing of tubular epithelial cells
Flattening and cytoplasmic simplification of tubular epithelial cells

H and E stain

RENAL TRANSPLANTATION
(Continued)

allograft vessels are sewn into the sides of the iliac vessels. After the vascular reconstruction is complete, the graft is immediately reperfused. The donor ureter is then anastomosed to the recipient's bladder. The abdomen is then closed, typically with no drains required.

IMMUNOSUPPRESSION

The fate of the graft depends on the response of the recipient's immune system. Thus immunosuppression is critical. A combination of azathioprine and corticosteroids was the first successful immunosuppression regimen, but the relative inefficacy of this regimen, combined with the adverse effects of high-dose steroids, led to poor outcomes in many patients. The introduction of cyclosporine in the 1980s brought about a dramatic improvement in outcomes and allowed for a significant expansion of kidney transplantation.

In the modern setting, there are several combinations of drugs that can be used to maintain immunosuppression in renal transplant recipients. The most common regimen includes a calcineurin inhibitor (tacrolimus, cyclosporine) and an antimetabolite (mycophenolate, azathioprine) or sirolimus. Many centers also include low-dose corticosteroids.

A delicate balance must be maintained between avoidance of allograft rejection and side effects, including opportunistic infections and malignancies. Infections in the first month after transplant typically include postoperative surgical infections, urinary tract infections, and pneumonias. At 1 to 6 months, opportunistic infections such as *Pneumocystis* pneumonia and CMV infection dominate. Further along, BK virus, human papilloma virus, CMV, and EBV-associated lymphoproliferative disease can appear.

POSTOPERATIVE PERIOD

Several complications, both surgical and immunologic, may cause delayed graft function (DGF) or failure of a previously functional graft. Therefore, it is essential that patients undergo regular monitoring with measurement of serum creatinine concentration. At some centers, surveillance biopsies are also performed either on a routine basis or in select patients at high risk for rejection.

The most probable causes of graft dysfunction depend on the amount of time that has passed since the transplantation.

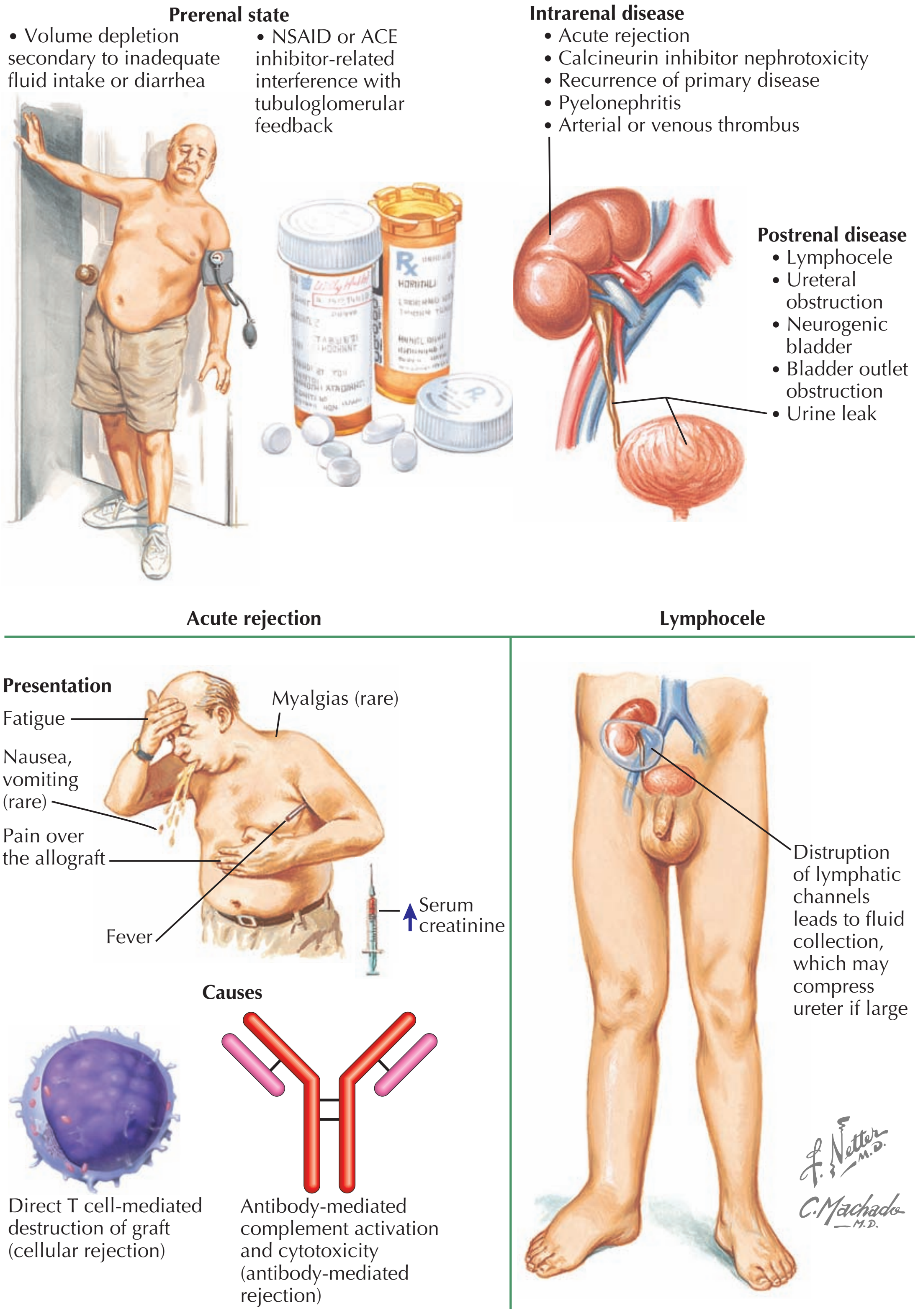
Immediate Postoperative Period. After a live donor transplant, the kidney begins functioning right away in roughly 95% of cases. After a deceased donor transplant, however, there may be some degree of DGF, which may last for days, weeks, or even months.

Hyperacute rejection occurs minutes to hours after transplantation, and it is often diagnosed in the operating room immediately after revascularization of the allograft. Such rejection reflects the presence of preformed antibodies that target antigens on the allograft, such as HLA class I proteins, HLA class II proteins, or ABO blood group antigens. A patient may become HLA-sensitized by previous blood transfusions, pregnancies, or prior transplants. No matter the cause, the presence of preformed antibodies leads to rapid

RENAL TRANSPLANTATION

(Continued)

Causes of Graft Dysfunction in Early Post-Transplant Period


Prerenal state
• Volume depletion secondary to inadequate fluid intake or diarrhea
• NSAID or ACE inhibitor-related interference with tubuloglomerular feedback
Intrarenal disease
• Acute rejection
• Calcineurin inhibitor nephrotoxicity
• Recurrence of primary disease
• Pyelonephritis
• Arterial or venous thrombus
Postrenal disease
• Lymphocele
• Ureteral obstruction
• Neurogenic bladder
• Bladder outlet obstruction
• Urine leak
Acute rejection
Presentation
Fatigue
Nausea, vomiting (rare)
Pain over the allograft
Fever
Myalgias (rare)
↑ Serum creatinine
Causes
Direct T cell-mediated destruction of graft (cellular rejection)
Antibody-mediated complement activation and cytotoxicity (antibody-mediated rejection)
Lymphocele
Distruption of lymphatic channels leads to fluid collection, which may compress ureter if large

immune complex formation, complement-mediated inflammation, and activation of the coagulation cascade with subsequent allograft thrombosis. The allograft is rapidly lost and must be removed. This complication is rarely seen in current transplantation due to preoperative crossmatch testing performed between the recipient serum and donor cells, as described previously.

In the immediate postoperative period, acute tubular necrosis (ATN) is the most frequent cause of DGF. Risk factors include prolonged cold ischemia times and older age of the donor. Patients with ATN are offered supportive care because spontaneous resolution after 1 or more weeks is common. ATN is a diagnosis of exclusion, however, and thus other potential causes of DGF must be ruled out, including prerenal state, thrombosis of the renal vessels, anatomic or functional obstruction of the urine collecting system, and urine leak.

Prerenal state, in which there is inadequate perfusion pressure in the allograft, may occur secondary to volume depletion or vasodilation. To avert this complication, patients should receive several liters of fluid in the operating room, which will help offset the vasodilation associated with anesthesia. If DGF occurs, the response to further fluid resuscitation should be included as part of the routine evaluation. Rarely, patients may experience volume depletion secondary to hemorrhage, possibly of the vascular anastomoses. If major postoperative bleeding is suspected, immediate surgical reexploration should be performed.

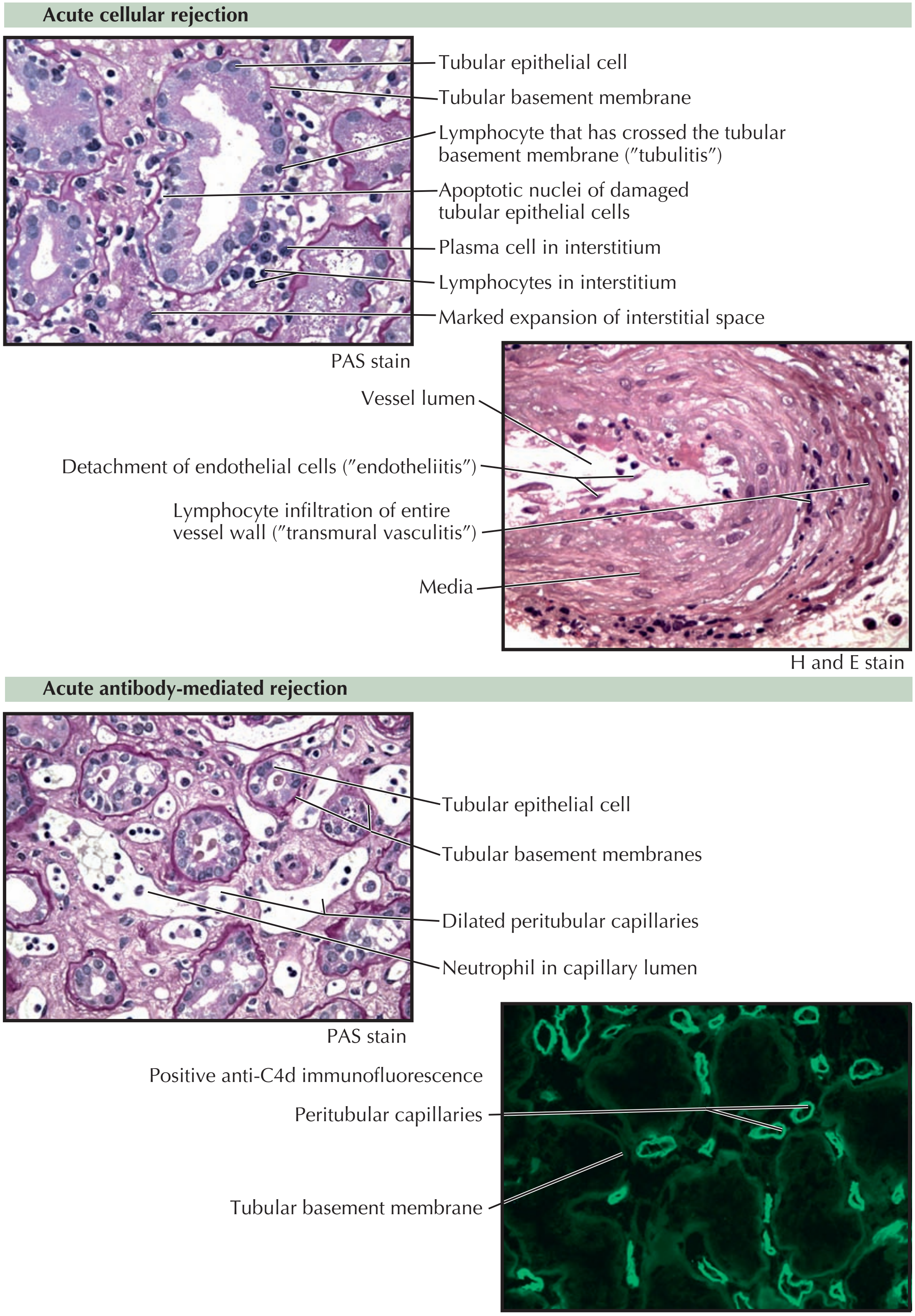
Primary thromboses of the renal vessels (i.e., not secondary to rejection) may occur secondary to surgical technique or, more often, a hypercoagulable state (e.g., antiphospholipid antibody). Both arterial and venous thromboses may cause sudden anuria; venous thromboses are also associated with pain around the allograft. Both kinds of thromboses can only be treated with immediate surgical reexploration, which usually reveals an infarcted graft that must be removed. Thromboses can be diagnosed with color Doppler ultrasound, which will reveal an absence of arterial and/or venous flow.

Obstruction of the urinary collecting system is another possible cause of delayed graft function. There are numerous possible causes, including benign prostatic hypertrophy, neurogenic bladder, blood clots in the ureter, tight ureterovesical anastomosis, and malpositioning/obstruction of a urinary catheter.

Finally, urine leak may present similarly to delayed renal function because it causes low urine output and, as a result of urine reabsorption, an elevation in serum creatinine and urea concentrations. Possible causes include ureteral infarction or failure of the ureterovesical anastomosis. Urine leaks can usually be diagnosed using ultrasonography or isotope renography. Stenting across the defect may be attempted, although surgical reconstruction may be necessary in some cases.

Early Post-transplant Period (1 Week to 6 Months). Many of the pathologies that cause DGF may also cause renal dysfunction in the early post-transplant period. Prerenal state, for example, may occur secondary to inadequate fluid intake, diarrhea, or use of drugs that impair tubuloglomerular feedback, such as ACE inhibitors or NSAIDs. In addition, renal vessel thromboses may not occur until several weeks post-transplantation.

Pathologic Findings in Acute Rejection of Kidney Allograft


Acute cellular rejection
Tubular epithelial cell
Tubular basement membrane
Lymphocyte that has crossed the tubular basement membrane ("tubulitis")
Apoptotic nuclei of damaged tubular epithelial cells
Plasma cell in interstitium
Lymphocytes in interstitium
Marked expansion of interstitial space
PAS stain
Vessel lumen
Detachment of endothelial cells ("endotheliitis")
Lymphocyte infiltration of entire vessel wall ("transmural vasculitis")
Media
H and E stain
Acute antibody-mediated rejection
Tubular epithelial cell
Tubular basement membranes
Dilated peritubular capillaries
Neutrophil in capillary lumen
PAS stain
Positive anti-C4d immunofluorescence
Peritubular capillaries
Tubular basement membrane

RENAL TRANSPLANTATION

(Continued)

Postrenal disease, such as urinary tract obstructions and urine leaks, may also occur during this period. In addition to the obstructions that may be seen immediately following the transplantation, patients may also develop lymphoceles, which occur secondary to disruption of lymphatic channels around the iliac arteries. Lymphoceles can cause thigh swelling and urinary frequency secondary to bladder compression. If very large, they may compress the allograft ureter and cause renal dysfunction. The diagnosis can be established using ultrasound or, as needed, analysis of a fluid aspirate. Symptomatic lymphoceles may be treated with a combination of ultrasound-guided drainage, followed by injection of sclerosing agents or, as needed, surgical marsupialization.

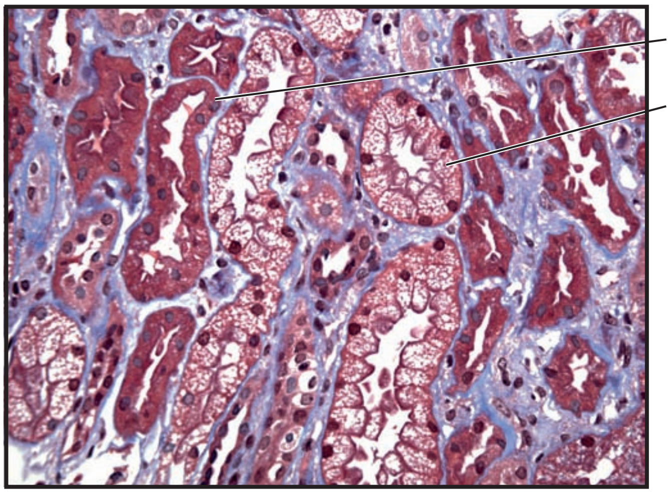
The other causes of early post-transplant graft dysfunction include various types of intrarenal disease, including acute allograft rejection (either cellular or antibody-mediated), calcineurin inhibitor nephrotoxicity, medication or contrast-associated nephrotoxic ATN, acute pyelonephritis, and recurrence of the primary renal disease.

Acute allograft rejection can be either cellular or antibody-mediated. It is the most frequent type of rejection, occurring in 10% to 15% of patients during the first year after transplant. Manifestations include a rapid loss in renal function, sometimes accompanied by low-grade fever and pain over the graft. More systemic signs of illness, such as nausea or myalgias, have become uncommon with the use of modern immunosuppression regimens. Acute rejection may occur as little as 1 week after transplantation but is typically seen after 1 to 3 months. It should be strongly suspected in a patient with declining renal function but reasonable plasma calcineurin inhibitor levels and no evidence of recurrent primary disease (i.e., no proteinuria or evidence of glomerular bleeding). Because the treatment strategies for cellular and antibody-mediated acute rejection are different, a renal biopsy is essential for making the distinction.

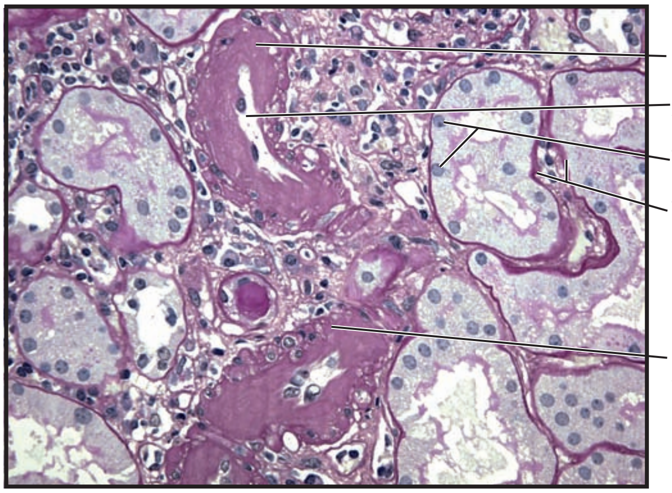
Acute cellular rejection results from an interaction between recipient antigen-presenting cells (APCs), recipient T cells, and MHC antigens on donor cells. The T cells become activated, resulting in the transcription of genes for cytokines and cytokine receptors, leading to inflammation in the allograft. Histopathologic findings include interstitial inflammation, predominantly by T lymphocytes, accompanied by tubulitis, which occurs when T cells cross tubular basement membranes and infiltrate tubular epithelium. Inflammation of arteries (endarteritis) may also be noted. It usually begins as endotheliitis, characterized by swelling and detachment of endothelial cells, as well as lymphocyte infiltration of the endothelial layer. In severe cases, transmural vasculitis may occur, in which lymphocytes infiltrate and inflame the entire thickness of the vessel wall. Acute cellular rejection can usually be treated with a pulse of high-dose corticosteroids or, in cases of steroid resistance, antilymphocyte antibodies.

Acute antibody-mediated rejection is less common than acute cellular rejection, and it may result from a previous exposure to a specific antigen, or from de novo reactivity and clonal expansion of reactive B cells. It typically occurs within 2 weeks of transplantation, and

HISTOPATHOLOGIC FINDINGS IN CALCINEURIN INHIBITOR NEPHROTOXICITY

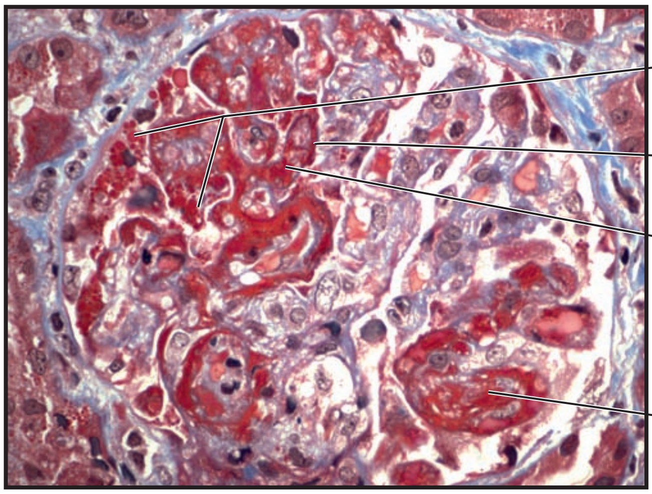

Normal tubular epithelial cells
Tubular epithelial cells with isometric vacuolization of cytoplasm

Trichrome stain


Diffuse hyaline deposits in arteriolar wall
Arteriolar lumen
Tubular epithelial cells
Tubular basement membranes
"Beaded" appearance of medial myocytes with significant hyaline deposition

PAS stain

Thrombotic microangiopathy


Podocytes (visceral epithelial cells) filled with protein droplets
Glomerular basement membrane
Glomerular capillary lumen filled with fibrin-rich thrombus
Fibrillar appearance of fibrin-rich thrombus

Trichrome stain

RENAL TRANSPLANTATION
(Continued)

the presentation is similar to acute cellular rejection. Patients are found to have antibodies that target donor HLA or ABO-group antigens. Histopathologic findings can range from a subtle form of tubular injury, similar to what is seen in ATN, to dramatic occlusion of glomerular capillaries by neutrophils and fibrin-rich thrombi. One of the most common histologic manifestations of acute antibody-mediated rejection is peritubular capillaritis, characterized by dilation of the interstitial capillaries and margination of leukocytes, most often a combination of neutrophils and lymphocytes. A helpful marker of acute antibody-mediated rejection is the presence of C4d within peritubular capillaries. C4d is a degradation product of complement factor C4 and can be detected using either immunofluorescence or immunohistochemistry. Acute antibody-mediated rejection can be treated with plasmapheresis to remove the antibodies and infusion of intravenous immunoglobulin.

Calcineurin inhibitor (CNI) nephrotoxicity may also occur in the early postoperative period, often secondary to drug-induced constriction of afferent arterioles. The diagnosis should be suspected in a patient with a supratherapeutic serum calcineurin inhibitor concentration in whom renal function improves after dose reduction. A lack of response to dose reduction, however, does not necessarily exclude CNI-related disease. Thus a biopsy is often required to make the distinction from acute rejection. If no significant pathologic changes are seen at biopsy, the CNI toxicity is assumed to be a predominantly hemodynamic effect. Several pathologic changes, however, are sometimes seen. CNI toxicity can affect tubules, where it causes isometric vacuolization of the epithelial cytoplasm. CNI toxicity can also affect vessels, where it causes hyalinosis of medial myocytes. These changes are best appreciated in afferent arterioles. Rarely, CNI toxicity can cause severe endothelial cell damage that results in thrombotic microangiopathy, characterized by fibrin thrombus formation in small arterioles and glomerular capillaries.

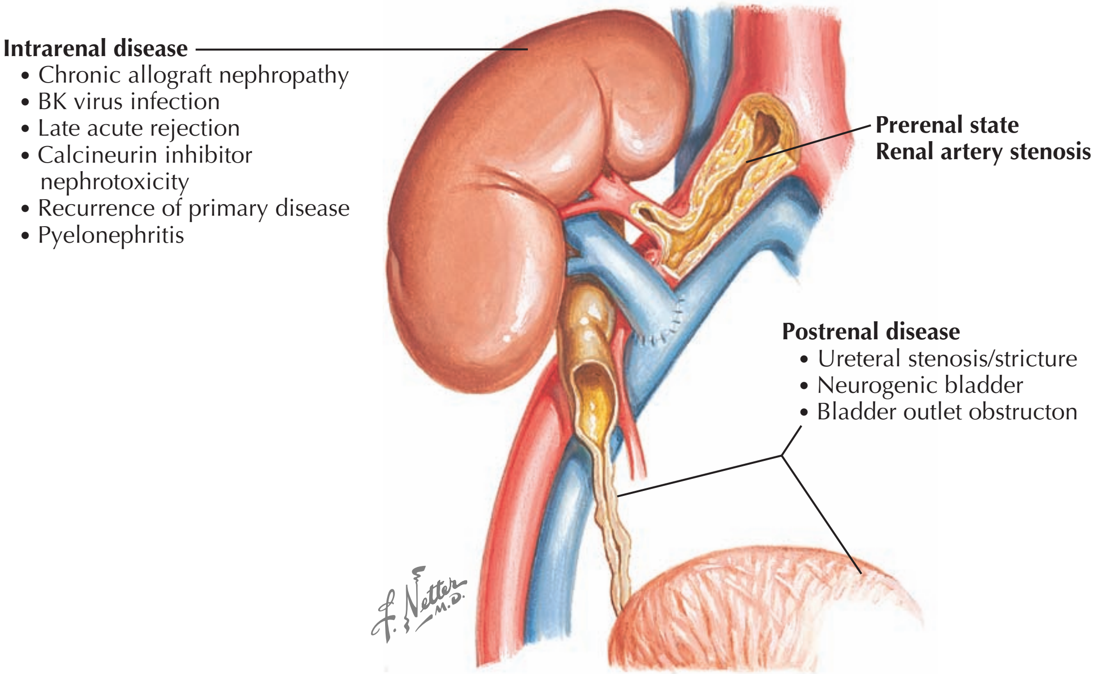
Numerous medications may cause nephrotoxic ATN in allografts, as they do in native kidneys (see Plate 4-3). Certain drugs, such as erythromycin, are especially nephrotoxic when administered along with calcineurin inhibitors because of their effects on hepatic metabolism.

Pyelonephritis may occur secondary to immunosuppression and frequent catheterization. Like acute rejection, it may present as fever and allograft pain. Urine dipstick and culture should be performed to assess for the presence of this complication.

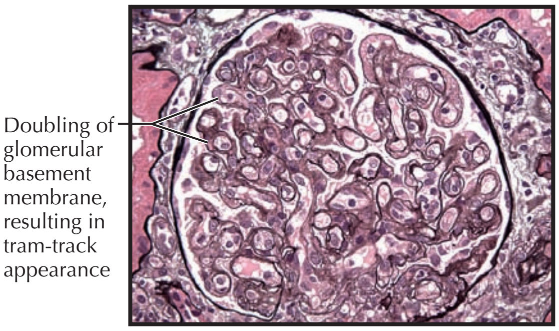
Recurrence of a primary renal disease, such as focal segmental glomerulosclerosis, may also occur. Although glomerular disease may sometimes be distinguished from rejection based on the presence of heavy proteinuria or glomerular bleeding (i.e., red blood cell casts or dysmorphic red blood cells) on urine sediment, biopsy is often required to make the distinction.

Late Post-Transplant Period (After 6 Months). Many of the problems that can occur in the early post-transplant period may also occur in the late post-transplant period, including prerenal state, CNI

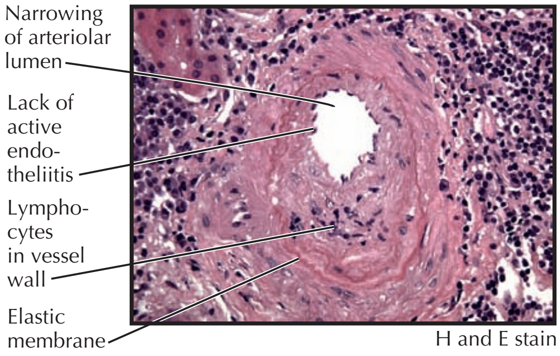
CAUSES OF GRAFT DYSFUNCTION IN LATE POST-TRANSPLANT PERIOD IN KIDNEY TRANSPLANTATION


Intrarenal disease
• Chronic allograft nephropathy
• BK virus infection
• Late acute rejection
• Calcineurin inhibitor nephrotoxicity
• Recurrence of primary disease
• Pyelonephritis
Prerenal state
Renal artery stenosis
Postrenal disease
• Ureteral stenosis/stricture
• Neurogenic bladder
• Bladder outlet obstructon
F. Netter M.D.

Chronic allograft nephropathy (histopathologic findings)

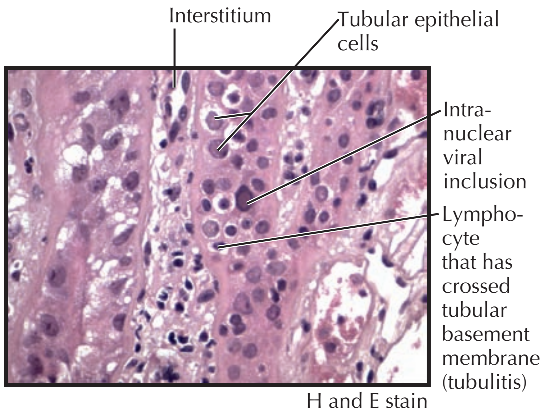

Doubling of glomerular basement membrane, resulting in tram-track appearance

Silver stain

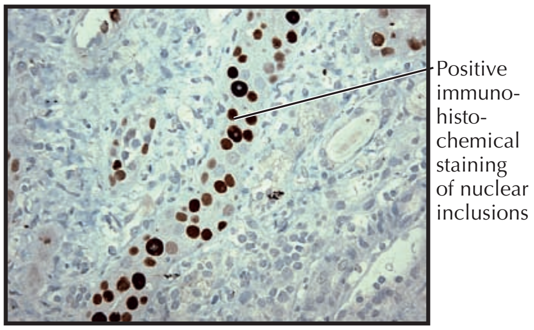

Narrowing of arteriolar lumen
Lack of active endotheliitis
Lymphocytes in vessel wall
Elastic membrane

H and E stain

BK virus infection (histopathologic findings)


Interstitium
Tubular epithelial cells
Intranuclear viral inclusion
Lymphocyte that has crossed tubular basement membrane (tubulitis)

H and E stain


Positive immunohistochemical staining of nuclear inclusions

Anti-SV40 immunohistochemistry

RENAL TRANSPLANTATION
(Continued)

nephrotoxicity, nephrotoxic ATN, pyelonephritis, recurrence of primary disease, and urinary tract obstruction. Late acute rejection may also occur in patients with inadequate immunosuppression or medication noncompliance. The other causes of late post-transplant graft dysfunction include chronic allograft nephropathy, BK virus infection, and renal artery stenosis.

Chronic allograft nephropathy, the most important cause of late allograft loss, is a poorly characterized phenomenon. Most pathologists use the term to encompass a myriad of structural and functional alterations related to chronic rejection that develop over the course of months and generally cause loss of the graft over a period of years. The major histologic findings include interstitial fibrosis, tubular atrophy, chronic arterial and arteriolar inflammation with luminal narrowing, and transplant glomerulopathy (which features doubling of the glomerular basement membrane, as in membranoproliferative glomerulonephritis).

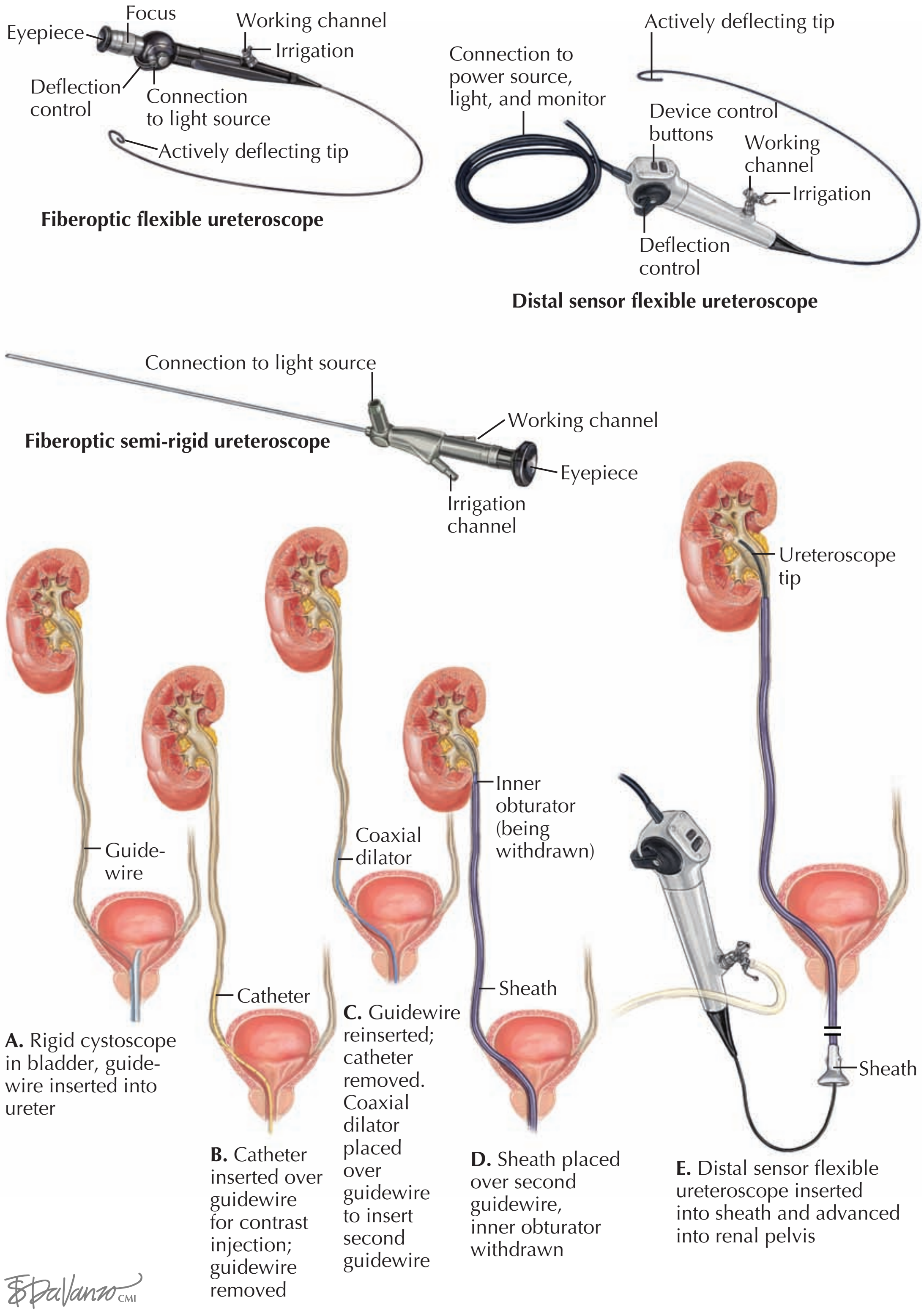
BK virus is a polyomavirus that infects many adults but only appears to cause disease in those who are immunosuppressed. It has a particular tropism for the urinary tract, where it can cause interstitial nephritis or ureteral stenosis. Urine microscopy reveals "decoy cells," which are tubular epithelial and urothelial cells infected with the BK virus. Since anti-BK antibodies are found in many individuals without BK-related disease, polymerase chain reaction (PCR) testing is performed to detect the virus itself in urine and blood, sometimes on a screening basis. A renal biopsy is performed if PCR is positive in the setting of renal dysfunction. Characteristic histopathologic findings include intranuclear inclusions within tubular epithelial cells, tubular injury, tubulitis, and interstitial inflammation. Anti-SV40 immunohistochemistry is performed to confirm the presence of viral antigen. Treatment usually consists of reducing the dosage of immunosuppressive therapies.

Renal artery stenosis (see Plate 4-36) may occur secondary to disease in either the donor or recipient vasculature. Possible causes include vascular trauma and atherosclerosis. Suggestive clinical features include hypertension, renal dysfunction that is worsened upon provision of ACE inhibitors, weakened femoral pulses, and a new bruit over the allograft. Percutaneous transluminal angioplasty may be required for severe cases (see Plate 10-17).

Prognosis. Despite the risks associated with the transplantation procedure and allograft rejection, the overall prognosis for patients who receive renal transplants is excellent. The graft survival rates for deceased donor kidneys are 89%, 78%, and 67% at 1, 3, and 5 years, respectively; meanwhile, the graft survival rates for living donor kidneys are 95%, 88%, and 80% at 1, 3, and 5 years, respectively.

Because of these positive outcomes, kidney transplantation is becoming widely practiced around the world. Improvements in organ access, donation, preservation techniques, immunosuppression, and management of disease progression will further improve outcomes and access to transplantation in the future.

URETEROSCOPY: DEVICE DESIGN AND DEPLOYMENT



Fiberoptic flexible ureteroscope

Distal sensor flexible ureteroscope

Fiberoptic semi-rigid ureteroscope

A. Rigid cystoscope in bladder, guidewire inserted into ureter

B. Catheter inserted over guidewire for contrast injection; guidewire removed

C. Guidewire reinserted; catheter removed. Coaxial dilator placed over guidewire to insert second guidewire

D. Sheath placed over second guidewire, inner obturator withdrawn

E. Distal sensor flexible ureteroscope inserted into sheath and advanced into renal pelvis

URETEROSCOPY

Ureteroscopy refers to the direct visualization of the ureter and renal pelvis using an endoscope. It is indicated for the treatment of numerous conditions, including renal and ureteral stones, ureteropelvic junction obstructions, ureteral strictures, and upper tract malignancies. It may also be performed to remove foreign bodies, such as a proximally migrated ureteral stent. Finally, it may be performed to evaluate abnormal urine cytology findings, filling defects on retrograde pyelography, or hematuria.

URETEROSCOPE DESIGN

Ureteroscopes are small endoscopes that can be either semirigid (minimal bending of the straight metal shaft) or flexible (with an actively or passively deflectable distal tip). Both types feature optics consisting of either fiberoptic bundles or, more recently, a distal sensor. All ureteroscopes have at least one working channel, which is used for irrigation and through which laser fibers, stone baskets, and other devices may also be deployed. The size (outer diameter) of a ureteroscope is given in the French scale (1 Fr = 0.33 mm).

Semirigid ureteroscopes are primarily used to diagnose or treat pathology in the mid to distal ureter (i.e., below the iliac vessels). They have a tapered distal tip and typically possess one large working channel or two smaller working channels. The advantages of semirigid ureteroscopes over flexible ureteroscopes include larger working channels, improved stability in the distal ureter, and easier ureteral access. Disadvantages include the potential for urethral trauma during ureteroscope insertion, as well the potential for ureteral trauma during intubation of the ureteric orifice and manipulation of the ureteroscope within the ureter.

Flexible ureteroscopes can be used to access any area of the upper urinary tract, but they are primarily used to access the proximal ureter (i.e., above the iliac vessels) and renal pelvis. Contemporary flexible ureteroscopes provide dual deflecting capability of approximately 120 to 170 degrees in one direction and 170 to 270 degrees in the other direction, controlled using a thumb-operated lever. At present, all flexible ureteroscopes have a single working channel. The flexibility of the ureteroscope decreases when an instrument is present in the working channel; however, small-diameter holmium laser fibers have been developed that are both flexible and durable, causing only minimal resistance during deflection.

TECHNIQUE

Before undergoing ureteroscopy, the patient should have a documented negative urinalysis and urine culture, so as to reduce the risk of urosepsis.

The majority of ureteroscopic procedures are performed in a specialized cystoscopy suite. The patient is placed in a dorsal lithotomy position, with the lower extremities in stirrups. Either general or regional anesthesia is employed.

The procedure is typically initiated by visualizing the bladder lumen with a cystoscope (see Plate 10-37) and then deploying a guide wire into the ureteric orifice. The guidewire may be placed with either a rigid or flexible cystoscope, depending on surgeon preference. Next, a ureteral catheter is inserted over the wire, and a retrograde pyeloureterogram is performed to evaluate the anatomy of the upper tract and provide a map for deployment of the ureteroscope.

After the ureteral catheter has been withdrawn, the ureteroscope can be deployed. A semirigid ureteroscope is inserted adjacent to the wire. The wire, which provides a map of the upper urinary tract, can remain in place throughout the procedure. A flexible ureteroscope, in contrast, is deployed over the wire. Once it is in position, the wire must be withdrawn from the

UReteroscopy *(Continued)*

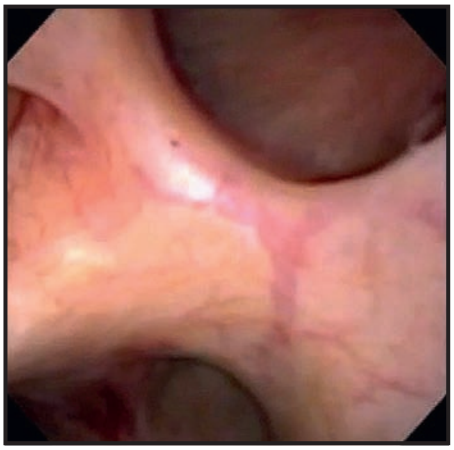
working channel to permit normal deflection and the introduction of devices. Thus before deployment of a flexible ureteroscope, a second guide wire is typically inserted to act as a “safety” wire, which remains present throughout the entire procedure and provides access to the upper urinary tract should normal anatomy become disrupted. To place a safety wire, a coaxial dilator/sheath is introduced over the first wire. The inner dilator is removed, the safety wire is introduced through the sheath, and then the sheath is removed.

When a flexible ureteroscope is being used, a ureteral access sheath can be placed early on to facilitate multiple insertions of the ureteroscope and limit the trauma associated with each passage. These sheaths also facilitate drainage of irrigation fluid, therefore permitting more frequent flushing of stone fragments and other debris created during lithotripsy procedures. Many different sheaths are available with a wide range of diameters and lengths. A ureteral access sheath is introduced over a wire. A tapered inner obturator in its lumen facilitates its passage through the ureter and helps dilate narrowed regions that would otherwise be difficult to traverse. Once the sheath is in position, the inner obturator and guide wire are removed. The ureteroscope can then be deployed through the sheath lumen. At the end of the procedure, the sheath is removed under direct vision.

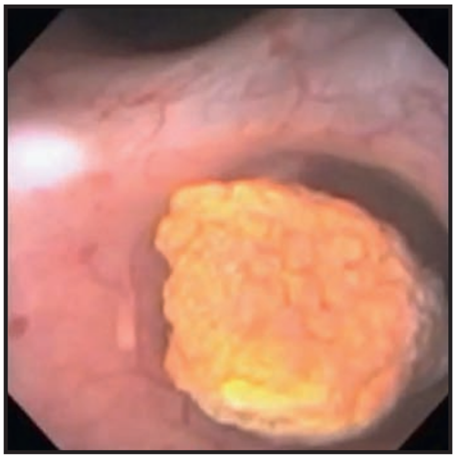
As the ureteroscope is advanced to the desired position, fluoroscopy is performed to monitor its progress in real time. Throughout the process, the urinary tract is irrigated with saline to facilitate ureteroscope passage and improve visualization. Irrigation pressure can be controlled by gravity, a compression bag, or hand-held pumps. If passage of the ureteroscope is difficult, the ureter may be dilated by passing a balloon dilator over the guide wire. Once the ureteroscope has reached the level of interest, various instruments can be introduced into the working channel to perform a diagnostic (e.g., biopsy) or therapeutic (e.g., ablation, stone basketing) procedure.

At the end of the procedure, a ureteral stent should be deployed if a ureteral access sheath has been used because the latter is associated with a risk of mucosal injury and postoperative ureteral edema. Ureteral stents are typically biocompatible polyethylene or silicone polymer devices. Most stents have curls at their proximal and distal ends, which help anchor them in the renal pelvis and bladder. In addition, most stents have small holes along their shaft to facilitate drainage. A ureteral stent may be placed through the working channel of a rigid cystoscope, or it can be deployed over a wire using fluoroscopic guidance. A plastic tube known as a stent pusher is used to ensure that the proximal curl reaches the renal pelvis. Care must be taken not to advance the distal curl into the ureter.

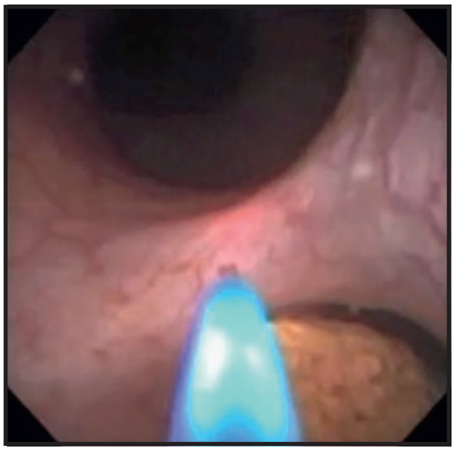
Stone Fragmentation and Extraction



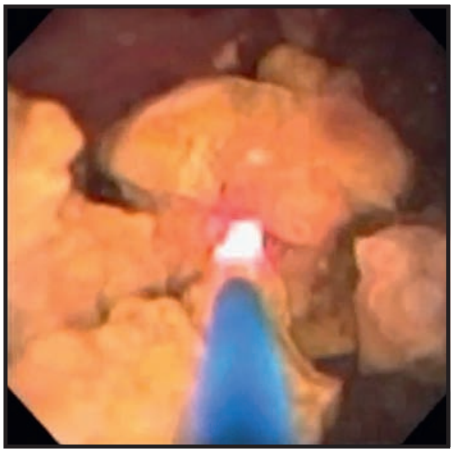
1. The flexible ureteroscope is advanced into the renal pelvis. The calices, seen here, are examined for stones.



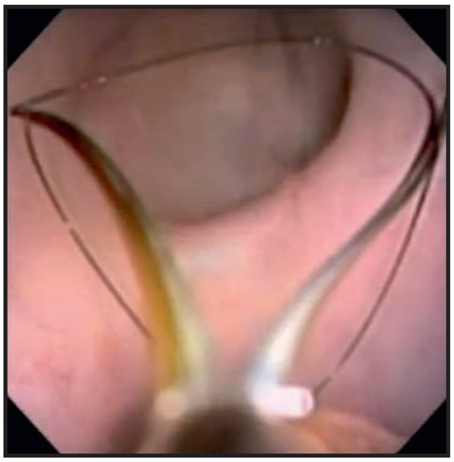
2. A stone is seen.



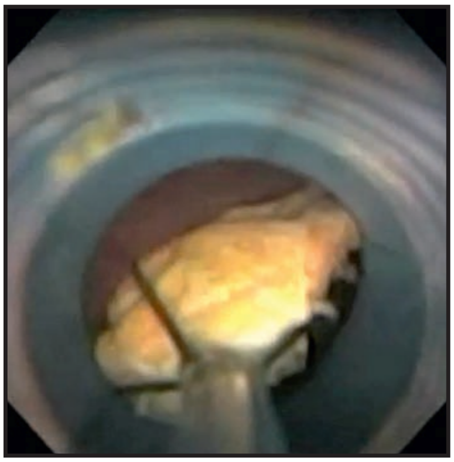
3. A holmium laser is introduced through the working channel of the ureteroscope.



4. The laser is used to fragment the stone into smaller fragments.



5. After fragmentation is complete, the laser is withdrawn, and a stone basket is introduced into the working channel.



6. The basket is used to remove the larger fragments, which are less likely to be spontaneously voided. Here, a fragment is seen entering the ureteral access sheath.

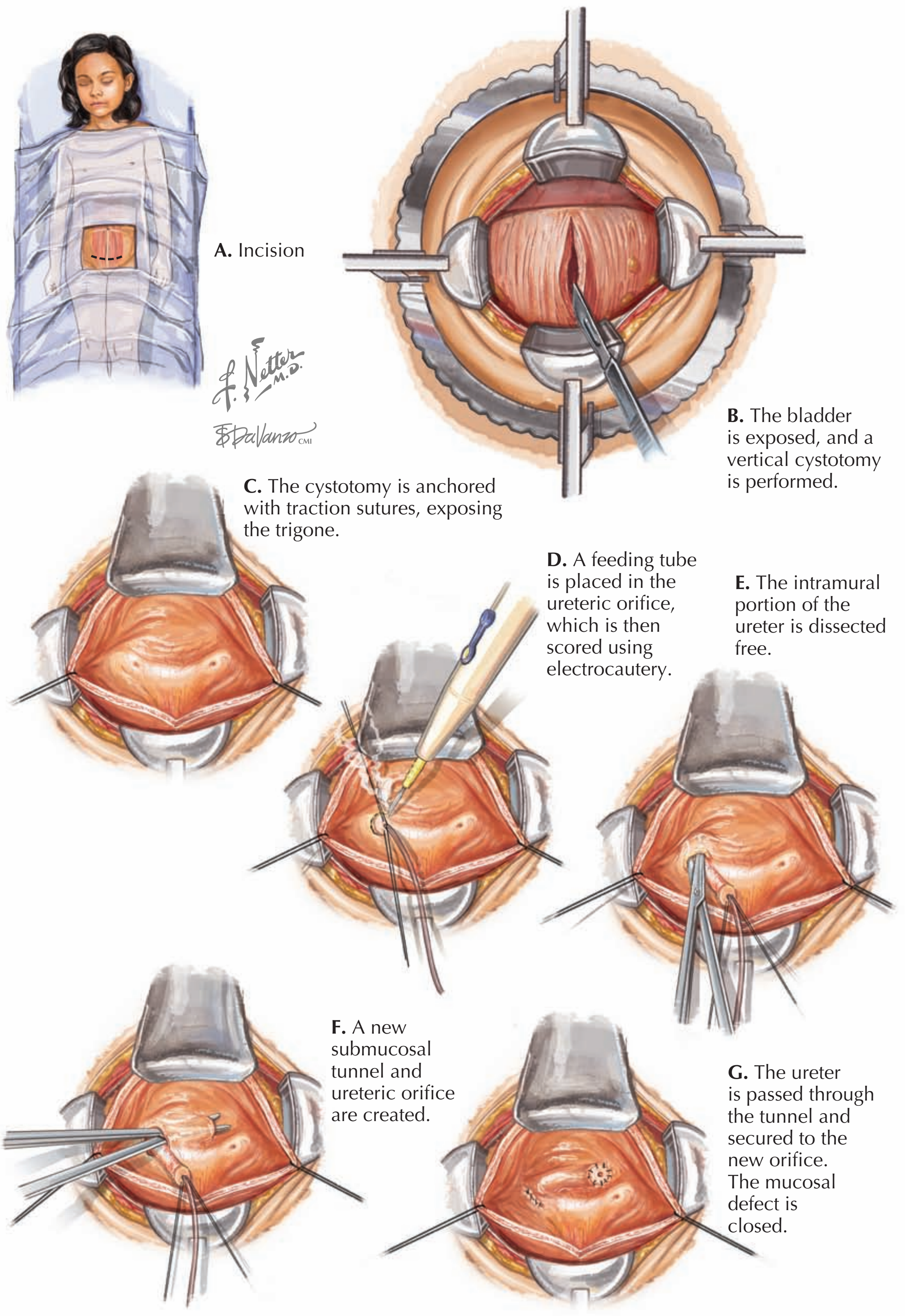
COMPLICATIONS

When performed properly, ureteroscopy is associated with few complications. The most common complications include stent colic (discomfort from the ureteral stent), transient hematuria, and urinary tract infection. The most concerning complication is ureteral perforation. Most cases of ureteral perforation, however, successfully heal with stent deployment alone. Ureteral avulsion is a rare complication of ureteroscopy that is most often repaired using open surgical technique.

FOLLOW-UP

Ureteroscopy is typically performed on an outpatient basis and does not require hospital admission. At present, there is no standard protocol for postoperative follow-up. A typical evaluation to rule out residual stone disease or stricture formation may include CT scan; radiograph of the kidneys, ureter, and bladder; or renal ultrasound. If a ureteral stent is placed after an uncomplicated ureteroscopy, it is usually removed 3 to 14 days later.

URETERAL REIMPLANTATION



A. Incision

B. The bladder is exposed, and a vertical cystotomy is performed.

C. The cystotomy is anchored with traction sutures, exposing the trigone.

D. A feeding tube is placed in the ureteric orifice, which is then scored using electrocautery.

E. The intramural portion of the ureter is dissected free.

F. A new submucosal tunnel and ureteric orifice are created.

G. The ureter is passed through the tunnel and secured to the new orifice. The mucosal defect is closed.

There are several invasive strategies for the management of high-grade vesicoureteral reflux (VUR, see Plate 2-21), and the cross-trigonal ureteral reimplantation is one of the most popular and effective techniques. In this procedure, the refluxing ureter is dissected free of its attachments to the bladder wall, then advanced through a new submucosal tunnel that extends toward the opposite side of the trigone. The significantly lengthened intramural segment prevents further reflux.

The surgery begins with a transverse incision approximately one fingerbreadth above the pubis to the lateral edges of both rectus muscles. The rectus fascia is incised transversely, and fascial flaps are raised. The rectus muscle bellies are longitudinally divided in the midline until the pubis is reached, then a self-retaining ring retractor is inserted to expose the bladder.

The peritoneum is identified and avoided, and the bladder is opened from the dome to just above the bladder neck. Traction sutures can be used to secure the inferior aspects of the cystotomy to the rectus fascia. The self-retaining ring retractor is repositioned to achieve a clear view of the trigone and ureteric orifices. Rolled moist gauzes are counted and placed into the dome of the bladder.

A 5-Fr feeding tube is placed into the orifice of the refluxing ureter and then secured using traction sutures at the 6- and 12-o'clock positions. The bladder mucosa is scored around the orifice in an oval shape using needle-tip electrocautery with a low cutting current. The plane of dissection is then established by incising the bladder wall perpendicular to the ureter at the 6-o'clock position of the orifice until the ureteral adventitia is reached. The intramural ureter is then circumferentially dissected free of its attachments using fine tenotomy scissors and a fine right angle clamp. In males, it is important to be cognizant of the nearby vas deferens.

The traction sutures and dissection sequentially release the intramural portion of the ureter until an adequate length for reimplantation is obtained, usually defined as four times the ureteral diameter. The dissection process often leaves a gap in the detrusor floor, which should be reapproximated to prevent formation of a diverticulum.

A new submucosal tunnel is then established between the mucosa and detrusor. Tenotomy scissors are introduced into the original hiatus (i.e., the site where the ureter first enters the bladder wall) and advanced under the mucosa toward the contralateral side of the trigone. Once a tunnel of adequate length has been created, a new ureteric orifice is created by incising the mucosa. Using the traction sutures to flatten the bladder floor facilitates this process.

The ureter is passed through the new tunnel, with care taken to avoid twisting, and then secured to the new orifice with a single stitch through the cuff of the distal end of the ureter, the bladder mucosa, and the detrusor muscle. A feeding tube is passed to confirm no twisting has occurred. The remainder of the cuff is sutured to the bladder mucosa with interrupted absorbable sutures. The gap in the bladder mucosa from the prior dissection is now closed with a running absorbable suture. The feeding tube is passed a final time to ensure patency. Stenting is not performed unless the ureter has been tapered (i.e., redundant ureteral wall has been removed because the ureter was severely dilated).

The gauzes are removed and counted, then the bladder is closed in two layers. The first is an absorbable running suture of the bladder mucosa, followed by a running absorbable suture of the seromuscular layer. The bladder is distended with saline through a Foley catheter to confirm a watertight closure. The rectus muscles are then reapproximated and the rectus fascia closed. The remaining fascial planes and skin are then closed.

Postoperatively, the patient should receive double the maintenance intravenous fluid rate for the first 12 to 24 hours, which will irrigate the bladder and ureteral anastomosis. The Foley catheter should remain in place for the first several days to facilitate healing of the cystotomy. After the catheter is removed, the patient should void frequently to maintain low bladder pressure. The routine use of postoperative VCUG to check for resolution of reflux has been abandoned. An ultrasound, however, should be obtained several weeks after the surgery to assess for possible hydronephrosis secondary to ongoing ureteral obstruction.

URETERAL RECONSTRUCTION

Reconstruction of the ureter is required if a segment has been removed during the treatment of trauma, stricture, stenosis, or other regional disease. Several different techniques are available, with the optimal choice depending on both the location and length of the excised segment.

DISTAL URETERAL DEFECTS

Ureteroneocystostomy is appropriate for small defects (<5 cm) in the distal ureter. It consists of reimplantation of the proximal ureteral end directly into the bladder (see Plate 10-35). The reimplantation should be performed with antireflux technique whenever possible; however, if the ureter end is not long enough to pass through a new submucosal tunnel, a refluxing orifice may be created instead.

A psoas hitch can be used to bridge a longer defect (up to 10 cm) in the distal ureter. This procedure involves mobilization of the entire bladder. The contralateral superior umbilical artery, and in some cases the entire contralateral bladder pedicle, may be ligated to permit such mobilization. An anterior cystotomy is performed, and the dome of the bladder is sutured to the psoas muscle on the side of the ureteral injury. Care must be taken not to injure the femoral or genitofemoral nerves. The ureteral end is then reimplanted into the bladder using antireflux technique when possible.

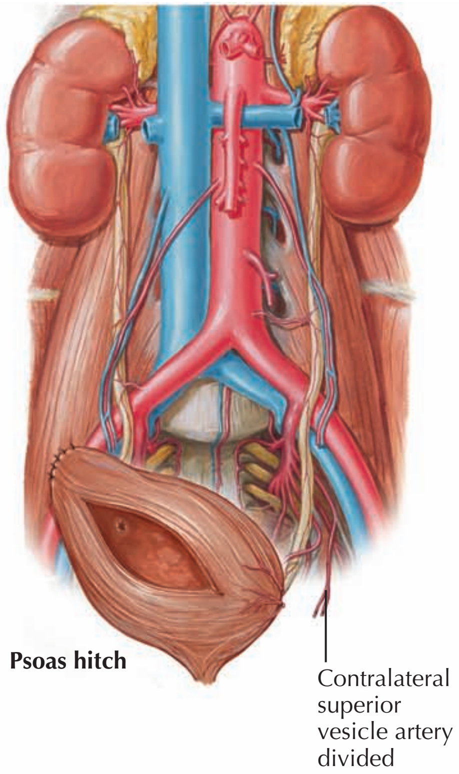
A Boari flap is reserved for more extensive defects in the mid and distal ureter (10 to 15 cm) that cannot be corrected with a psoas hitch. The bladder is mobilized as in a psoas hitch, and then a full-thickness flap is created from the bladder wall in the territory of the superior vesical artery or one of its branches. The width of the flap base should be at least three times greater than the length of the flap to ensure an adequate vascular supply. The flap is then tubularized around a small-diameter catheter and anastomosed to the proximal end of the ureter in end-to-end fashion. The distal aspect of the reconstructed tube is sutured to the psoas tendon to prevent migration of the bladder and ensure a tension-free reconstruction. The patient will experience a significant reduction in bladder capacity following this procedure.

UPPER OR MIDURETERAL DEFECTS

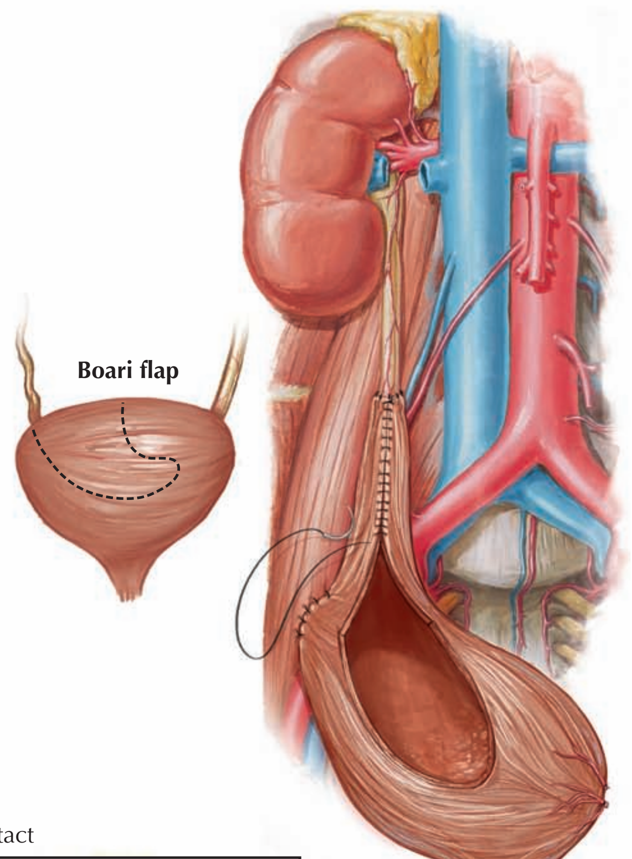
A ureteroureterostomy is typically performed to bridge short defects in the midureter. It consists of anastomosis of the two free ends of a ureter after a short segment (2 to 3 cm) has been excised. The proximal and distal ureteral ends are spatulated and anastomosed over a stent in a water-tight and tension-free fashion.

Transureterostomy may be performed for larger defects in the midureter. In this procedure, the free proximal end of the ureter is anastomosed to the contralateral ureter in end-to-side fashion. The major drawback of the procedure, however, is that the crossed ureter becomes very difficult to access from an endoscopic approach. Therefore, it is avoided in patients with a history of nephrolithiasis or urothelial carcinoma, in whom ureteroscopic access is often desired. In addition, the procedure requires exposure and intentional injury of the contralateral ureter, both of which can cause unexpected complications.

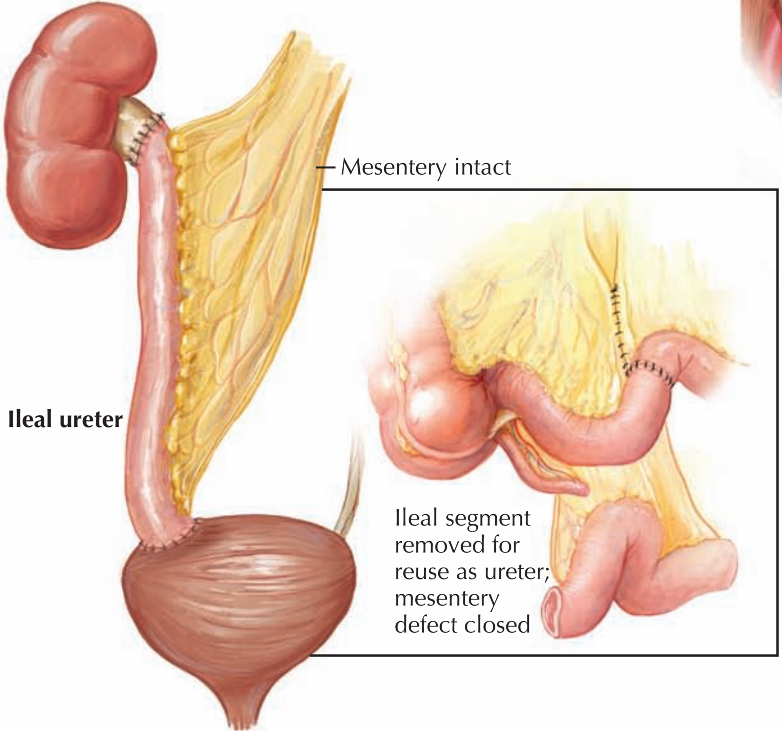
A renal descensus can help bridge large upper ureteral defects. Renal descensus requires entry into the renal fascia and complete mobilization of the kidney until its only attachments are the vascular pedicle and ureter. The kidney is rotated medially and inferiorly, then sutured to the retroperitoneal musculature. A ureteroureterostomy can subsequently be performed.



Psoas hitch



Boari flap

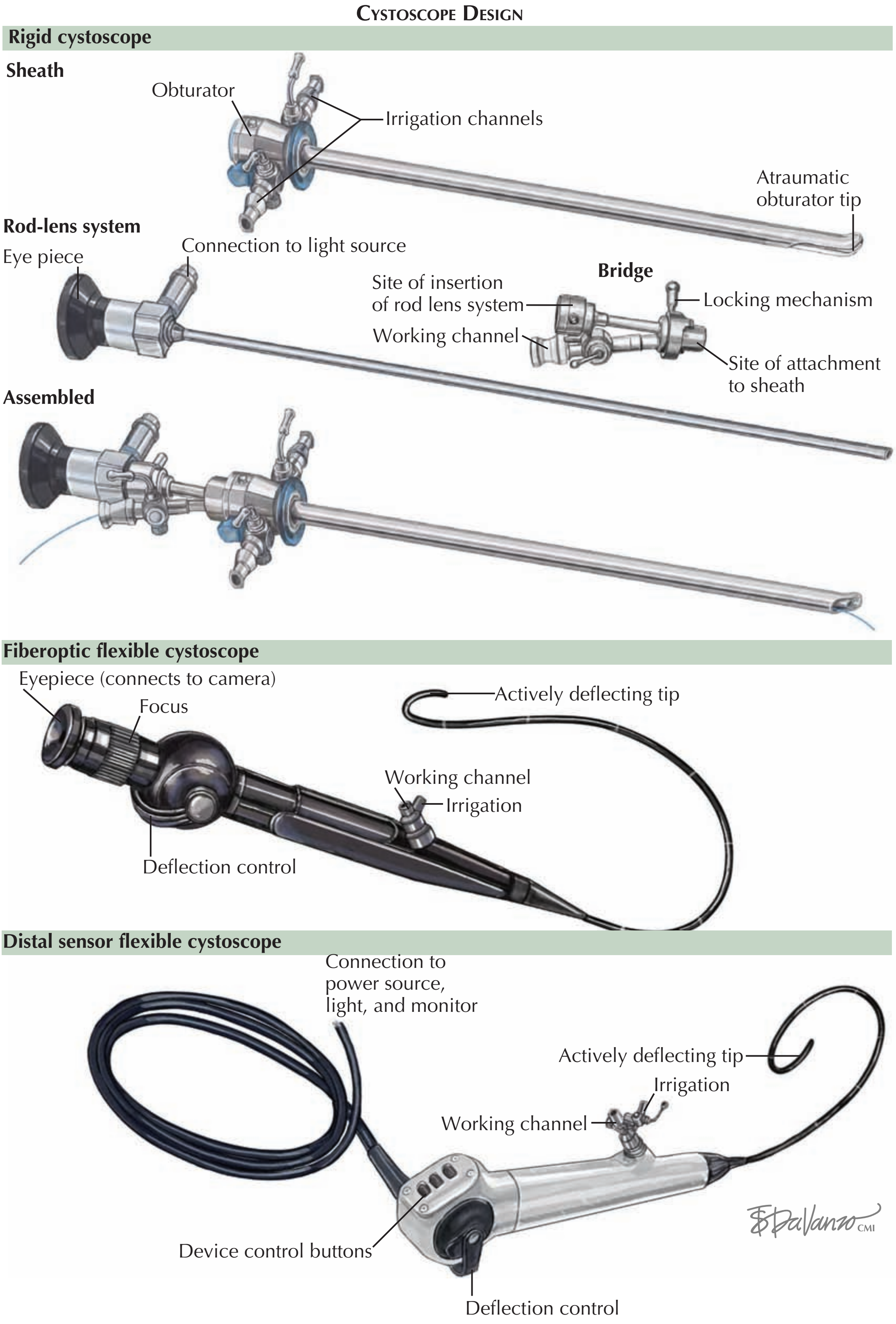


Ileal ureter

Mesentery intact
Ileal segment removed for reuse as ureter; mesentery defect closed

An ileal ureter, which introduces the bowel into the urinary tract, is used for wide ureteral defects or other surgically complex cases that require more drastic reconstruction efforts. Patients with baseline renal insufficiency (serum creatinine ≥2), liver dysfunction, bladder dysfunction, radiation enteritis, or inflammatory bowel disease should not undergo this procedure. After the patient has undergone adequate bowel preparation and oral antibiotic treatment, a segment of ileum (located at least 15 cm from the ileocecal valve) is excluded with its vascular supply intact. The segment is then anastomosed to the renal pelvis and posterior wall of the bladder. It is important to maintain normal proximal-to-distal orientation of the ileal segment so that peristalsis occurs in the correct direction. The open ends of bowel created by the ileal resection are reanastomosed to restore continuity, and the mesenteric window is closed to prevent bowel strangulation.

Finally, autotransplantation may be employed as a last resort in the case of very large ureteral defects. In this procedure, the kidney is harvested as in a donor nephrectomy, then anastomosed to the patient's own iliac vessels, as in a recipient operation.



CYSTOSCOPE DESIGN

Rigid cystoscope
Sheath
Obturator
Irrigation channels
Atraumatic obturator tip
Rod-lens system
Eye piece
Connection to light source
Site of insertion of rod lens system
Working channel
Bridge
Locking mechanism
Site of attachment to sheath
Assembled
Fiberoptic flexible cystoscope
Eyepiece (connects to camera)
Focus
Actively deflecting tip
Working channel
Irrigation
Deflection control
Distal sensor flexible cystoscope
Connection to power source, light, and monitor
Actively deflecting tip
Irrigation
Working channel
Device control buttons
Deflection control

CYSTOSCOPY

Cystoscopy refers to the direct visualization of the anterior and posterior urethra, bladder neck, and bladder mucosa using an endoscope. This procedure is performed both to evaluate the lower urinary tract and to establish access to the upper urinary tract (see Plate 10-33). Common indications include microscopic or gross hematuria, obstructive voiding symptoms, surveillance of a known urinary tract malignancy, inability to urinate following surgery for incontinence, and removal of a foreign body.

CYSTOSCOPE DESIGN

Cystoscopes are available in a variety of sizes and may be either rigid or flexible in design. The size (outer diameter) of a cystoscope is given in the French scale.

Rigid Cystoscopes. A rigid cystoscope has a long metal sheath, bridge, and rod-lens system. The sheath is the outer cover through which the rod-lens system is inserted. It remains within the bladder when the rod-lens system must be removed or exchanged. It also contains the port for infusion of irrigant fluid, which helps maintain continuous visualization. The sheath is inserted into the bladder with an obturator in its lumen, which has an atraumatic tip to ensure safe passage through the urethra. "Visual" obturators contain a lumen for the lens, which permits direct visualization of the insertion process, whereas "nonvisual" obturators lack such a lumen.

The sheath attaches to a bridge, which contains an opening for the rod-lens system and also contains the working channel through which instruments such as biopsy forceps, hand-held graspers, wires, catheters, and cautery probes may be inserted.

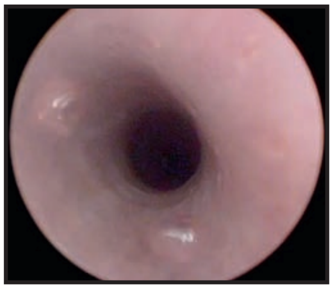
The rod-lens system contains an objective lens at its tip that transmits an image to the eyepiece. Lenses are designed at different angles (0, 12, 30, and 70 degrees) so that different aspects of the urinary tract can be visualized. When a different lens is required, the rod-lens system is withdrawn from the sheath and exchanged for another one. In the past, the urologist would look directly through the eyepiece, but in contemporary practice a camera is attached so the image can be transmitted to a monitor.

Advantages of rigid cystoscopes over flexible cystoscopes include a larger sheath diameter for better irrigation, as well as a larger working channel. Because of these features, it is easier to perform procedures such as retrograde pyeloureterography and bladder biopsy. Rigid cystoscopes, however, are uncomfortable for patients and thus require regional or general anesthesia. In addition, the patient must be in lithotomy position.

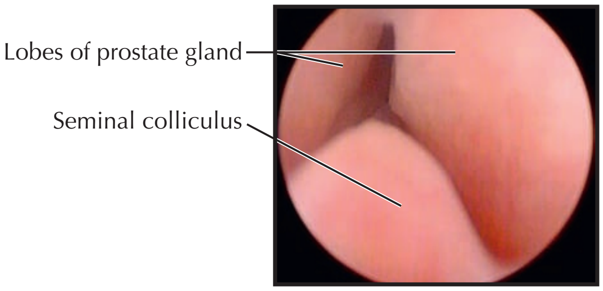
Flexible Cystoscopes. Flexible cystoscopes have small, soft, flexible shafts; a working channel; and an irrigation port. The optics consist of either fiberoptic bundles or, more recently, a distal sensor (either a complimentary metal oxide sensor or charge coupled device). Flexible cystoscopes have deflective capabilities of up to 220 degrees, controlled by a thumb-operated lever. Unlike a rigid cystoscope, a flexible cystoscope is a single unit and does not come in multiple pieces. Flexible cystoscopes are more comfortable than rigid cystoscopes, and in some cases they can be deployed without

CYSTOSCOPIC VIEWS

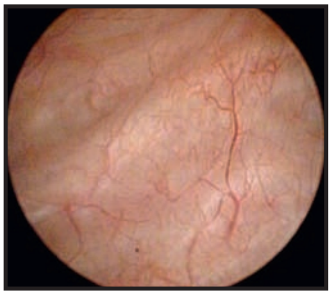
Normal-appearing bladder



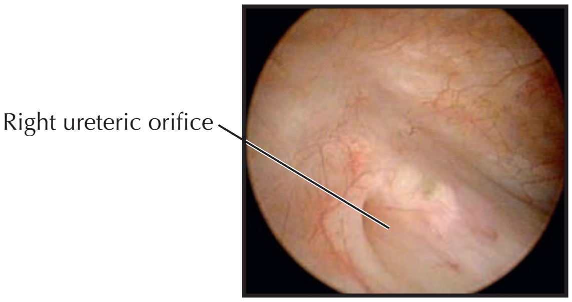
1. The penile urethra appears normal during initial cystoscope insertion.



2. The prostate gland and seminal colliculus are seen from within the prostatic urethra.

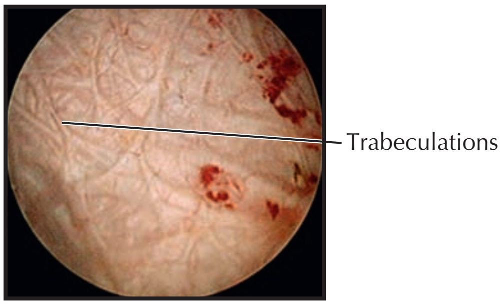


3. The bladder is reached, revealing normal-appearing mucosa.

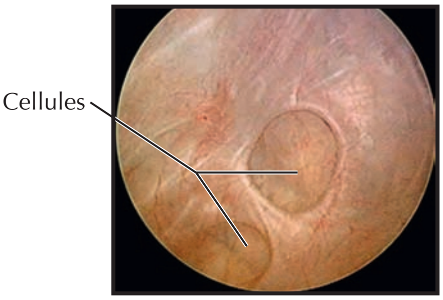


4. The ureteral orifices are visualized during inspection of the entire mucosal surface.

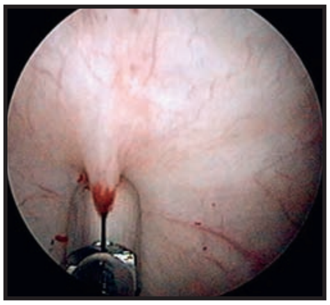
Abnormal-appearing bladder



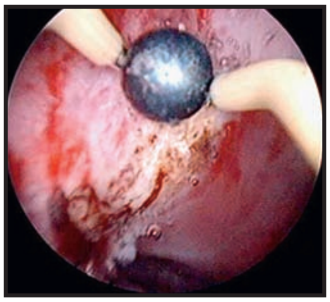
1. This patient with hematuria has multiple areas of abnormal mucosa. Trabeculations indicate chronic outlet obstruction.



2. Cellules are seen, also consistent with chronic outlet obstruction.



3. Directed and random biopsies of the bladder mucosa are acquired using biopsy forceps.



4. Areas of active bleeding are fulgurated using a rolling ball device.

CYSTOSCOPY *(Continued)*

anesthesia. In addition, the deflection capabilities improve visualization of the bladder mucosa and allow the cystoscope to be deployed with the patient supine.

PREOPERATIVE ASSESSMENT AND TECHNIQUE

Before undergoing cystoscopy, the patient should have a recent negative urinalysis and urine culture, so as to reduce the risk of urosepsis. If even bacteriuria is present, the patient should be treated with culture-directed oral antibiotics, and the cystoscopy should be rescheduled.

Rigid cystoscopy is performed in an operating room under regional or general anesthesia. Flexible cystoscopy, in contrast, is often performed in the office, with local intraurethral anesthetic (lidocaine/HCl 2% jelly) provided several minutes before the procedure.

The patient's genital area is sterilized and draped. If the urethral meatus is stenotic, a urethral dilator can be deployed first. Either saline or sterile water can be used for irrigation; however, if electrocautery is planned, either water or another nonconductive irrigant should be used.

When placing a rigid sheath in a female, a nonvisual obturator may be used. In contrast, when placing a rigid sheath in a male, a visual obturator should be used with a 30-degree lens to examine the urethra. The penis should be placed on gentle stretch to straighten the urethra and facilitate cystoscope passage. Some men with large prostates or an elevated bladder neck may require gentle manipulation of the cystoscope to access the urinary bladder.

Once the cystoscope is in the bladder, the trigone and ureteral orifices are visualized. Next, the entire mucosal surface is examined. If a rigid cystoscope is being used, a 30-degree lens permits visualization of the trigone and posterior wall, whereas a 70-degree lens offers visualization of the lateral walls, anterior wall, and dome of the bladder. If a flexible cystoscope is being used, active deflection of the tip can be performed to visualize all of these areas. All urologists should have a thorough routine to ensure no areas of mucosa are missed. During this process, care should be taken not to overfill the bladder with irrigation fluid, as this can increase the risk of postoperative urinary retention.

Following inspection of the mucosal surface, various procedures may be performed by inserting instruments into the working channel. After these procedures are completed, the cystoscope is removed, and the bladder is drained through either the rigid sheath or a Foley catheter.

COMPLICATIONS

Complications of flexible and rigid cystoscopy include urinary tract infection, postprocedural hematuria and dysuria, and transient urethral pain. The creation of a false passage and urethral trauma may also occur, but these complications are more common with rigid cystoscopes. In addition, a rigid cystoscope is more traumatic in men with enlarged prostates, who may experience postprocedural hematuria even with gentle passage of the cystoscope under direct vision.

TRANSURETHRAL RESECTION OF BLADDER TUMOR

Bladder cancer is typically discovered during the evaluation of gross or microscopic hematuria. Transurethral resection of a bladder tumor (TURBT) offers both diagnostic and therapeutic benefits. First, it provides a gross sample that can be sent for histopathologic evaluation to determine tumor stage and grade. Second, it removes macroscopic disease from the bladder and can be a curative treatment for superficial tumors.

Therefore, all bladder tumors, whether primary or recurrent, should undergo resection at the time of initial cystoscopic evaluation. Resection should not be deferred to a subsequent intervention because there is a risk of tumor upstaging with each event.

If pathologic analysis reveals a high-grade superficial stage tumor (Ta or T1), the standard of care is to perform re-resection because the risk of disease persistence and possible upstaging is high. Invasive tumors, in contrast, require more definitive treatment, such as cystectomy and/or chemotherapy.

TECHNIQUE

A negative urine culture should be documented before the procedure. The patient should be placed in dorsal lithotomy position using leg stirrups. General anesthesia should be administered. It is important to induce complete paralysis because the monopolar current used during tumor resection can stimulate the obturator nerve, causing a sudden and robust muscle contraction that can injure the surgeon or cause accidental bladder perforation.

A bimanual examination should be performed to assess for the presence of palpable disease in the prostate and bladder wall, which would influence the clinical stage. Next, a rigid cystoscope (see Plate 10-37) is placed in the urethral meatus and advanced through the urethra into the bladder. As the cystoscope is being inserted, the urethral mucosa is carefully examined under direct vision. Frequent irrigation improves vision during this process.

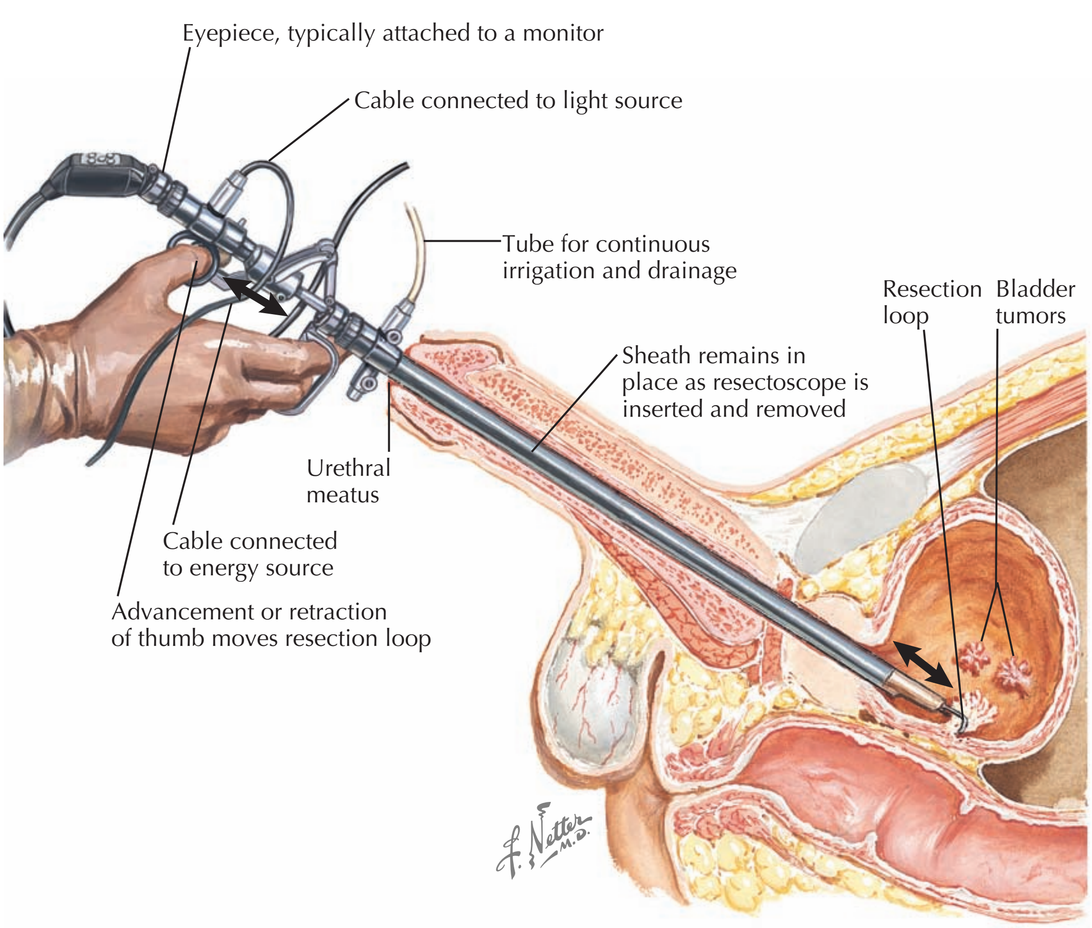
Once the cystoscope tip is in the bladder, urine is aspirated into a syringe for cytologic analysis. Performing several flushes of the syringe generally improves the cell yield. A retrograde pyeloureterogram is performed by intubating the ureteric orifices with small (6 or 7 Fr) ureteral catheters and injecting each one with 3 to 5 mL of contrast material.

After these initial tests have been completed, the systematic evaluation of the bladder mucosa begins. A 30-degree lens is first used to evaluate the urethra, trigone, and posterior wall of the bladder. A 70-degree lens is then used to evaluate the lateral walls, dome, and anterior wall of the bladder.

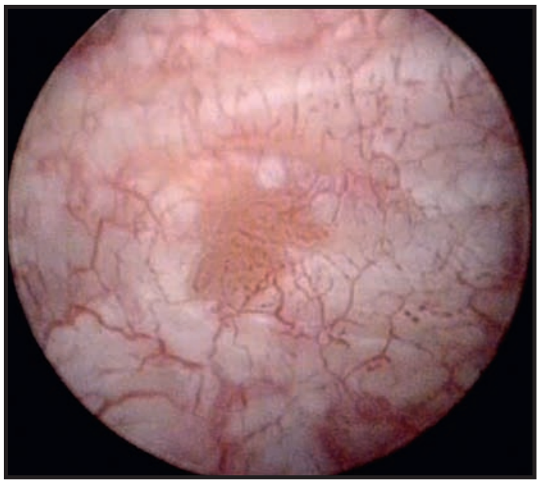
Once the entire mucosal surface has been examined and all tumors and abnormal-appearing areas have been identified, the cystoscope is removed in exchange for a resectoscope (using the 30-degree lens). Most resectoscopes have a large enough diameter to permit continuous flow and suction of irrigation fluid, which both improves visualization and stabilizes the bladder wall. The resectoscope is connected to an energy source that is applied to the bladder mucosa through a resection loop. The surgeon performs thumb movements to advance or retract the loop across the mucosal surface, while the application of energy is controlled with a foot pedal. Resection should begin with removal of the tumor's superficial exophytic portions, followed by removal of its deeper layers, until bands of detrusor

TRANSURETHRAL RESECTION OF A BLADDER TUMOR: EQUIPMENT AND PROCEDURE

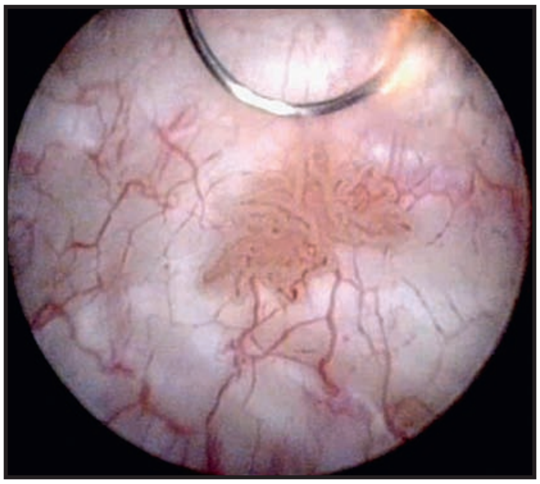
Equipment


Eyepiece, typically attached to a monitor
Cable connected to light source
Tube for continuous irrigation and drainage
Resection loop
Bladder tumors
Sheath remains in place as resectoscope is inserted and removed
Urethral meatus
Cable connected to energy source
Advancement or retraction of thumb moves resection loop

Procedure



1. During examination of the entire bladder mucosa with the cystoscope, a small papillary tumor is seen.



2. The resectoscope is introduced, and energy is applied through the resection loop to incise the mucosa adjacent to the tumor.

TRANSURETHRAL RESECTION OF BLADDER TUMOR *(Continued)*

fibers can be visualized. For smaller tumors, a single sweep of the loop may be adequate. To permit accurate staging, it is imperative that enough tissue be obtained to capture the muscularis propria.

When tumors are encountered at the bladder dome, it may be difficult to maneuver the resectoscope in a manner that permits safe resection. In such cases, suprapubic pressure can help bring the dome closer to the wire loop. In addition, slowing the flow of irrigant fluid will reduce bladder distention and bring the dome closer to the level of the urethra.

The resected tumor fragments should periodically be removed and placed intact in specimen jars. After resection is complete and all fragments have been removed, the resection sites must be examined again. The edges of each site should be cauterized, and hemostasis should be confirmed with the irrigation turned off. A Foley catheter should be inserted if there is an obvious area of perforation, an extensive area of resected urothelium, or a potential source of postoperative bleeding.

In addition to the wire loop resection technique described above, one can also obtain bladder tissue by inserting cold cup biopsy forceps into a standard cystoscope. Small bladder tumors or sites of abnormal-appearing urothelium can be directly grasped and simply pulled off of the bladder wall. The biopsied sites should be cauterized until hemostasis is achieved. This technique is especially useful when random bladder biopsies are required, as when carcinoma in situ is suspected, there is positive urine cytology but no visible tumor, or partial cystectomy is being considered.

COMPLICATIONS

In addition to the standard complications related to general anesthesia, TURBT may also cause bladder perforation, bleeding (with postoperative hematuria and clot retention), and injury to a ureteral orifice that requires temporary ureteral stent placement.

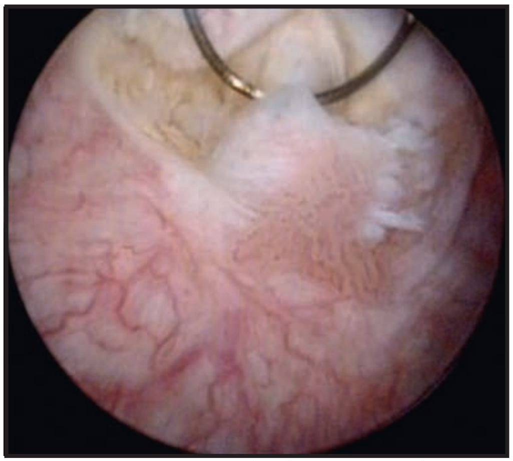
In the event of a bladder perforation, a Foley catheter should be inserted to decompress the bladder and facilitate healing. If the dome of the bladder has been perforated, however, open exploration and repair may be required, especially if there is evidence of bowel injury or peritoneal irritation. In most cases, however, catheter drainage is still adequate, and the risk of tumor cells seeding the peritoneum is low.

Ureteric orifice injuries are typically intentional and occur when a nearby tumor is being resected. Indeed, a tumor resection should always be complete, even if it results in resection of the ureteric orifice. If pure cutting current is used, however, patients generally suffer no long-term sequelae as long as a ureteral stent is temporarily placed.

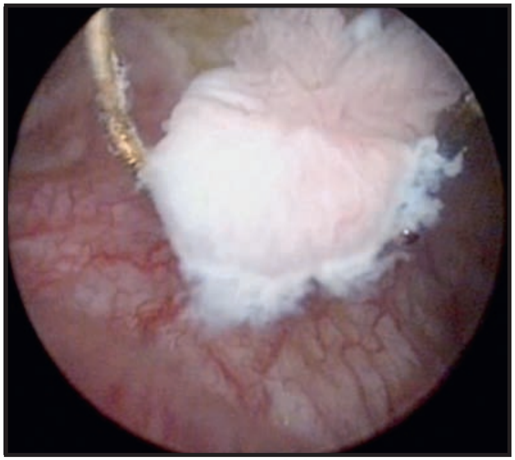
FOLLOW-UP

Patients undergoing TURBT generally do not require hospitalization and can be discharged after a short period of postoperative recovery. In the event of a more extensive resection that requires catheter placement, however, the patient is admitted overnight to monitor urine output and hematuria. The Foley catheter can usually be removed the next day, provided that there is no ongoing hematuria. Likewise, patients suspected of having postoperative bleeding, which carries the potential for clot retention, should also be hospitalized and monitored until the hematuria abates.

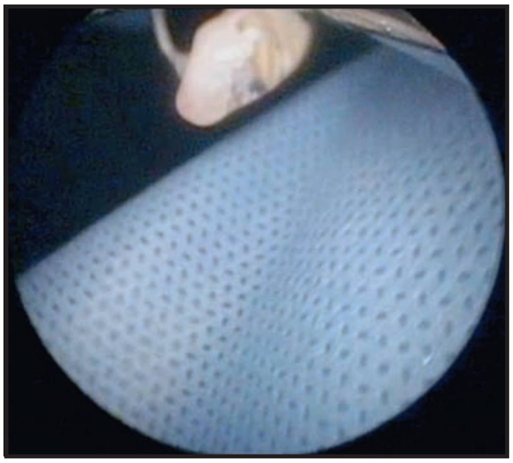
TRANSURETHRAL RESECTION OF A BLADDER TUMOR: PROCEDURE (CONTINUED)



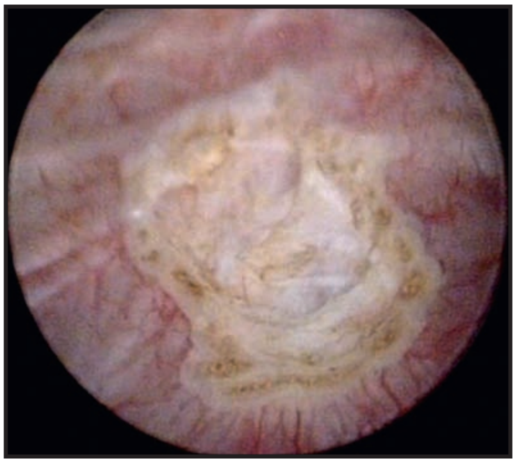
3. As resection proceeds, the tumor and surrounding mucosa can be seen separating from the underlying detrusor muscle.



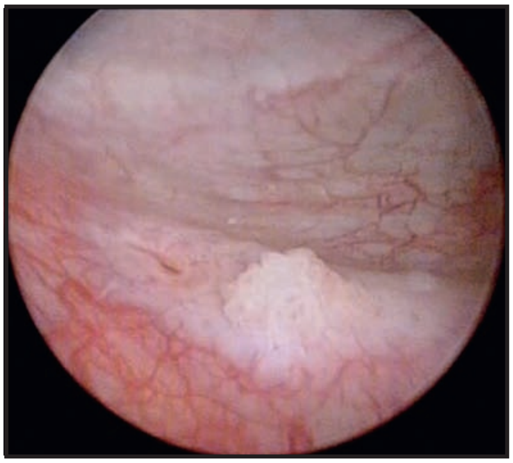
4. Resection continues until the tumor and adjacent mucosa are completely removed. Multiple passes may be required for larger tumors.



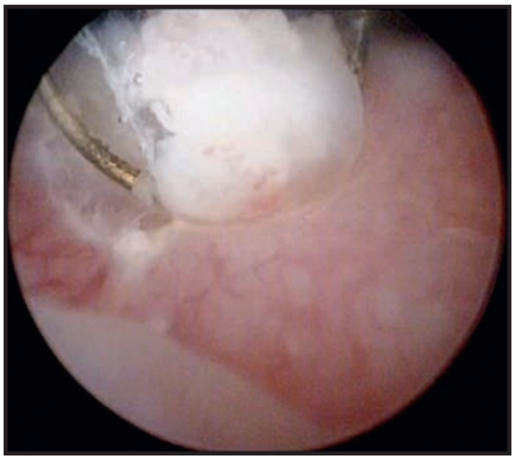
5. The specimen is withdrawn intact from the bladder and sent for pathologic examination.



6. The edges and bed of the musosal defect are further coagulated until all bleeding is controlled.



7. In this patient, another tumor had been visualized adjacent to the ureteric orifice.



8. This tumor, and all additional tumors, are resected as described above.